

**Neurocognitive and psychosocial late effects of
cranial radiotherapy in adult survivors of childhood
and adolescent cancers**

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**D.Clin.Psy. thesis (Volume 1), 2018
University College London**

UCL Doctorate in Clinical Psychology

Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Overview

This thesis examines the late effects of cranial radiotherapy in adult survivors of childhood cancers. Part 1 is a systematic literature review which aims to extend previous research by summarising the neurocognitive outcomes associated with the specific effects of cranial radiotherapy up to 34 years after completing treatment. Results indicated that cranial radiotherapy has greater effects on memory, processing speed, and attention than intelligence and general executive functions. Younger age at diagnosis and higher radiotherapy dosage were also associated with increased risk of adverse neurocognitive outcomes in adulthood.

Part 2 is an empirical paper which evaluates neurocognitive and psychosocial late effects of cranial radiotherapy within a specific subgroup of survivors of adolescent cancers. Adult survivors reported generally positive social adjustment, and IQ scores and levels of depression and anxiety were comparable to the normal population. Total radiotherapy dosage and receiving additional chemotherapy significantly predicted IQ. However, findings must be interpreted with caution, and the need for larger longitudinal studies with sufficient statistical power to fully characterise enduring deficits and determine factors that place survivors at greatest risk is discussed.

Part 3 is a critical appraisal of the research process which discusses issues of project development and the theoretical and methodological limitations inherent in studying the specific effects of cranial radiotherapy. The concept of post-traumatic growth and its applications to the current findings are also considered.

Impact Statement

The prognosis of childhood cancers has improved considerably in recent decades due to significant advances in medical technology. In particular, the inclusion of radiotherapy in the treatment protocols of many different cancers has been attributed to increased survival rates. Consequently, research into childhood cancers has broadened to examine the long-term outcomes associated with treatments such as cranial radiotherapy, referred to as late effects.

The present thesis contributes to this expanding area of research by investigating populations that have received little attention to date. Firstly, the systematic review explores neurocognitive outcomes in a cohort of survivors of childhood brain tumours and acute lymphoblastic leukaemia treated on early radiotherapy protocols in the 1980s, who are now moving into middle adulthood. Although radiotherapy is no longer routinely given to children with acute lymphoblastic leukaemia, this review represents the first opportunity to examine outcomes more than ten years following irradiation. Adult survivors who received cranial radiotherapy in childhood and adolescence up to 34 years previously were identified to be at increased risk for neurocognitive dysfunction, especially in domains of memory, attention, and processing speed. Understanding the effects of childhood cancer in adulthood is crucial in designing healthcare services to support an ageing population of survivors, and suggestions of early-onset dementia also indicate the need for continued clinical follow-up and research in this cohort. Moreover, knowledge of likely deficits and risk factors revealed in this review may be important for researchers developing treatments that use radiation as they strive to reduce neurotoxicity whilst maintaining treatment effectiveness.

Secondly, the empirical paper also provides a unique contribution to the existing literature, owing to its focus on neurocognitive and psychosocial late effects in adult survivors of adolescent cancers treated with cranial radiotherapy. Historically, the adolescent population has not been differentiated from childhood cancer survivors despite distinct developmental, cognitive, and neurological differences. The present results may therefore provide the first of many incremental steps in research towards understanding the effects of cranial radiotherapy across the lifespan in greater detail. This endeavour remains important as radiotherapy treatments continue to evolve, for example, with the increasing use of proton beam radiotherapy. The observed lack of impairment within current participants may be representative of a protective effect of receiving cranial radiotherapy during adolescence on later functioning, however, low power to detect small effects within the present sample limits the ability of this thesis to draw these conclusions. Radiotherapy dosage and receiving additional chemotherapy were also found to be significant predictors of lower IQ scores. Although further research is needed to clarify and extend current findings, this information could potentially be useful for oncology departments for use in treatment planning with adolescents, for example, in optimising dosage, and deciding whether to administer concurrent treatments such as chemotherapy. In the least, it is hoped that the promising findings of this exploratory study will inspire further research, including longitudinal and prospective studies, to address the limitations often encountered in this complex area of research.

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Acknowledgements

First and foremost, I would like to thank my supervisors, Professor Chris Brewin and Dr Daniel Glazer, for their kind encouragement, patience, wisdom, and emotional support over the past three years.

I would also like to thank to the psychology team at the specialist teenage and young adult oncology service, especially Eve Twivy, for their support with recruitment, and the Teenage Cancer Trust for their generous contribution towards the research.

Special thanks also go to my work colleagues for their advice and compassion, especially over the last few months.

Most importantly, I would like to say a huge thank you to my partner, Cameron, for his unwavering support and belief in me, and to my family, friends and fellow trainees for their understanding and encouragement, without which this thesis would not have been possible.

Finally, I would like to thank all the participants who volunteered their time and shared their experiences as part of this research.

Part 1: Literature Review

Neurocognitive outcomes in long-term survivors of childhood cancers treated with cranial radiotherapy: A systematic review

Abstract

Aims: Although widely-reported in the paediatric literature, the effects of cranial radiotherapy (CRT) have only recently started to be investigated in adult survivors of childhood cancers. The present systematic review aimed to determine the effects of CRT on cognitive functioning many years after treatment, and further elucidate the influence of multiple risk factors on neurocognitive outcomes in this population.

Methods: A systematic search of PsycINFO and Web of Science databases resulted in 21 published studies meeting predefined criteria, split into two groups according to cancer type.

Results: Findings across five key domains of cognitive functioning were reviewed; intelligence, memory, attention, processing speed, and general executive functions. Three risk factors (age at diagnosis, time since treatment, CRT dose) were also evaluated, and anatomical correlates of CRT across included studies considered.

Conclusions: Despite difficulty differentiating the effects of CRT from other treatments and risk factors, several studies suggested that CRT is more likely to have unique enduring effects on memory, attention, and processing speed than intelligence and general executive functions. Younger age at diagnosis and higher doses of CRT were associated with increased risk of adverse neurocognitive outcomes in adulthood, whilst few studies suggested any effect of time since diagnosis.

Introduction

Leukaemia, central nervous system (CNS) tumours, and lymphomas are among the most common malignant diseases presented in childhood, accounting for 29%, 26%, and 11% of all childhood cancers, respectively (Siegel, Miller, & Jemal, 2017).

Cranial radiotherapy (CRT) is a critical component of the treatment protocols for these cancers and has undoubtedly contributed to improved chances of survival.

However, as survival rates have improved, attention has been turned to the long-term effects of treatments, including the widely-reported effects on neurocognitive functioning¹. Despite a large literature examining the effects of CRT on the brain and cognition, there is ongoing controversy regarding its effects.

Cranial radiotherapy (CRT) in current and historic cancer treatment protocols

CRT uses ionising radiation to control or kill malignant cells. Although the exact therapeutic mechanism of CRT is still under investigation, current evidence suggests that radiation damages the DNA in cancerous cells, preventing reproduction and leading to eventual cell death (Hawley, 2013). CRT can be used as a definitive treatment, or adjunctively to target microscopic spread after surgery or chemotherapy (Snider & Mehta, 2016). Conventional external beam radiotherapy, which uses photons, is the most commonly used form, and total dose is usually administered in multiple fractions over time. The number of fractions varies depending on the type of cancer being treated, and is usually administered over a period of 2-7 weeks. The

¹ The term 'neurocognitive outcomes' is a broad term is used by many authors referring to specific late effects of treatment. Other terms including 'neurocognitive functioning', 'cognitive outcomes', 'cognitive functioning', 'cognitive late effects', 'cognitive sequelae' and 'neuropsychological functioning' have the same meaning and are used interchangeably throughout this review.

unit of radiation dose is known as a Gray (Gy), which refers to the amount of energy that is absorbed per unit mass. CRT is typically administered in fractions smaller than 2Gy, often given once daily (Tadman & Roberts, 2007; Tobias & Hochhauser, 2009).

The literature suggests that whole-brain and craniospinal radiotherapy have been used as methods of treating CNS cancers as early as the 1930s (Fischer & Holfelder, 1930). CRT was first implemented to attempt to eradicate deposits found in the brain and spinal cord seeded from primary cerebellar tumours, which were originally discovered in post-mortems of untreated brain tumour patients (Paterson & Farr, 1953). Later, in the 1960s, researchers at St Jude Children's Research Hospital began to experiment with incorporating CRT into treatment protocols for acute lymphoblastic leukaemia (ALL) (Aur et al., 1971; George et al., 1968). CRT was given early in remission based on theory developed from mouse studies which proposed that CNS radiation may eradicate clinically undetectable leukemic cells and prevent the development of secondary CNS leukaemia and relapse (Aur, Simone, Hustu, & Verzosa, 1972). The results of these studies indicated that combination 24Gy CRT and chemotherapy (intravenous methotrexate) was effective in preventing CNS relapse (Aur et al., 1972; Hustu, Aur, Verzosa, Simone, & Pinkel, 1973). However, reports of significant toxicity, infection, endocrine dysfunction, and cognitive decline started to emerge in the 1980s which led to a paradigm shift in the treatment of ALL; CRT was gradually replaced with contemporary therapeutic protocols which consist of intensified intravenous and intrathecal chemotherapeutic drugs and do not routinely include CRT (Pui et al., 2004; Simone, 2006).

Concerns over the potential long-term cognitive effects of CRT as a treatment for brain tumours (especially medulloblastoma) also began to arise as survival rates improved (Edelstein et al., 2011). CRT continues to be used to treat many brain tumours and current protocols prescribe maximal surgical resection, risk-based CRT (which usually involves targeting the entire craniospinal axis with an additional boost to the primary tumour site), and adjuvant chemotherapy (Gottardo & Gajjar, 2006). Radiotherapy regimens for paediatric brain tumours typically include higher total doses than for non-CNS cancers, and range between 45 and 65Gy depending on age and tumour factors (The Royal College of Radiologists, 2016). Consequently, more recent research has focused on identifying risk factors and modifying treatments in an attempt to reduce risk of neurocognitive impairment where possible (e.g. Duffner, 2004).

Late effects of CRT

The long-term impact of CRT on neurocognitive outcomes in childhood cancer survivors has been extensively studied, and many reviews have evaluated the literature to date across diagnoses. In contrast to the acute effects of CRT, which include fatigue, nausea, and pain, and resolve within weeks of treatment completion, late effects do not emerge immediately (Tadman & Roberts, 2007). Existing reviews suggest that children treated with CRT in ALL are at increased risk for significant cognitive sequelae one year or more following treatment (Duffner, 2004; Madan-Swain & Brown, 1991) and children who receive CRT for brain tumours are even more vulnerable than ALL survivors (Duffner, 2004; Roman & Sperduto, 1995). Specifically, cognitive deficits have been suggested across domains of intellectual functioning, academic achievement, memory, attention, and processing speed for

medulloblastoma survivors (Palmer, Reddick, & Gajjar, 2007) and samples of mixed CNS tumours (Mulhern, Hancock, Fairclough, & Kun, 1992; Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004). More rigorous reviews in paediatric brain tumour survivors employing meta-analytical (Robinson, Fraley, Pearson, Kuttesch, & Compas, 2013) and systematic (Wolfe, Madan-Swain, & Kana, 2012) approaches found significant deficits in overall cognitive ability and attention, working memory, processing speed, and general executive functions for survivors treated with CRT.

Despite the relative abundance of reviews which conclude adverse neurocognitive outcomes in survivors of brain tumours and ALL resulting from CRT, Armstrong, Gyato, Awadulla, Lustig, and Tochner (2004) describe the damaging effects of CRT as “more elusive and less robust than has been generally appreciated” (p.82).

Namely, there are a great number of confounding factors in this area of research which make interpretation of neurocognitive data difficult and question the validity of conclusions about the specific effects of CRT. Many risk factors for cognitive deterioration following CRT have been identified, including: tumour type, size, location, use of chemotherapy, hydrocephalus requiring shunt, and time since treatment, with younger age at diagnosis, and higher CRT dose being possibly the most well-documented (Armstrong et al., 2004; Duffner, 2010; Edelstein et al., 2011; Hoppe-Hirsch et al., 1990; Mulhern et al., 2004; Mulhern et al., 2005; Robinson et al., 2013; Ullrich & Embry, 2012). Although less consistently investigated, other risk factors such as female gender, treatment-related complications, and relapse have also been suggested to predict cognitive impairment (Ellenberg et al., 2009; Krull, Brinkman, et al., 2013; Schuitema et al., 2015).

Armstrong et al. (2004) further suggest that the failure of most studies to isolate the effects of CRT is due to feasibility rather than poor study design. Indeed, although the present review seeks to examine the specific effects of CRT on neurocognitive outcomes, it is impossible to account for the many patient and treatment-related risk factors and their complex interactions entirely. This review will attempt to address the influence of several widely-reported risk factors on neurocognitive outcomes following CRT treatment including cancer type, dosage, age at diagnosis, and time since diagnosis.

Neurocognitive outcomes in adulthood

Whilst prior literature has provided valuable information concerning the effects of CRT in the few years following treatment, it has been limited so far by the age of the participants involved and the follow-up intervals used. Given that CRT was only more widely used as treatment for cancer from the 1980s onwards, research to date has tended to examine neurocognitive outcomes in survivors after a maximum of ten years, with the majority of studies examining childhood cancer survivors fewer than five years post-treatment. Accordingly, little is known about neurocognitive sequelae of CRT for childhood cancers in adulthood. Since brain development continues well into adulthood (Giedd et al., 1996; Huttenlocher, 1979), it is logical to assume that the extent of impairment may change as survivors mature.

Previous studies that evaluated survivors up to ten years post-treatment have suggested that cognitive decline is progressive over time (e.g. Duffner, 2004; Hoppe-

Hirsch et al., 1990), or decline is steep in the first few years post-treatment and is then more gradual (Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004).

Modelling used to estimate the rate of change in IQ in medulloblastoma patients treated with CRT has produced estimates that vary from -2.05 to -4.30 points per year (Palmer et al., 2001; Palmer et al., 2003; Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001; Walter et al., 1999). However, it is not possible to predict decline across the lifespan from these studies, highlighting the need for research over longer periods.

Recent studies examining childhood brain tumour and ALL survivors treated with CRT 20 years or more after treatment suggest that cognitive decline continues (Harila, Winqvist, Lanning, Bloigu, & Harila-Saari, 2009; Krull, Zhang, et al., 2013). It has also been suggested that irradiated survivors are at increased risk for early-onset dementias as their cognitive profiles have been shown to be consistent with accelerated ageing (Armstrong et al., 2013; Daams et al., 2012; Schuitema et al., 2013). However, it is important to distinguish whether these declines represent true deficits in functioning at this stage post-treatment. Longitudinal studies that identify CRT-induced declines in IQ have also found that abilities may initially remain within normal limits if individuals with high premorbid IQ (and greater associated cognitive reserves) are included (e.g. Edelstein et al., 2011; Krull, Zhang et al., 2013). It is also possible that survivors treated with CRT may experience poorer neurocognitive outcomes than those treated with other modalities, but remain within normal limits.

Rationale and aims of the review

To date, no review has investigated the effects of CRT specifically on adult survivors of childhood cancers. Although CRT is no longer routinely given to children with ALL, studies of these survivors have important implications for the large population of long-term survivors treated under previous protocols. Moreover, a review in this area may help to further current knowledge of CRT as it is applied in current treatment protocols. Given the suggestion that some neurocognitive functions, such as IQ, may be subject to CRT-induced decline but remain within normal limits, the effects of CRT are mostly evaluated with respect to other treatment modalities, but also inspected with regards to impairment² in this review.

The present review aims to answer the following questions:

1. What are the cognitive late effects of CRT in adult survivors of childhood cancers across the major domains of cognitive functioning?
2. Is there an effect of cancer type i.e. does CRT have different effects on CNS cancers compared to non-CNS cancers?
3. Are outcomes also related to: a) age at diagnosis, b) time since treatment, c) CRT dosage?
4. What are the effects of CRT on brain structures and activity?

² The terms ‘impairment’ and ‘impaired’ will be used throughout the review to indicate that scores fell below the average range when compared to healthy population norms. This differentiation is made as it is possible that studies may demonstrate a specific adverse effect of CRT, such that those receiving CRT show poorer scores than those treated with chemotherapy and/or surgery, whilst remaining within normal limits.

Method

Inclusion and exclusion criteria

Inclusion criteria were established according to the review objectives and using the population, intervention, comparator, and outcome tool (Stone, 2002), as follows:

1. Publications:
 - a. Published in a peer-reviewed journal between 1900 and 2018
 - b. Available in English
2. Population:
 - a. Studies of long-term survivors of childhood cancers, defined as those who were diagnosed and treated for cancer before the age of 18 years old, were at least 16 years old at the time of assessment, and completed treatment at least five years prior to participation
3. Design:
 - a. Case-control, cross-sectional, and longitudinal designs
4. Interventions and Comparator/Control
 - a. Include a cohort of cancer survivors who received CRT
 - b. Involve a comparative group or include analysis partialling out effects of CRT
5. Outcome
 - a. Include one or more measures of cognitive functioning in adulthood

No date limitation was imposed, to include cohorts of participants treated on previous treatment protocols. Inclusion criteria explicitly allowed for different cancer diagnoses where CRT was included in the treatment protocol, to allow for comparison within the current review. Records were excluded if they were reviews, meta-analyses, or commentaries. Due to the specific nature of the review question,

studies that included a mixed population of children and young adults were excluded unless children and adult outcome data was analysed separately. Animal studies were also excluded.

Search strategy

Systematic searches were conducted using PsycINFO (1806 to January 2018), and Web of Science databases (all databases; 1900 to January 2018). The following combination of keywords was used across all databases: *(radiotherapy or radiation) AND (cancer) AND (cognitive or cognitive function* or neuropsych* or attention or executive or memory or language or motor or coordination) AND (long-term or dysfunction* or deficit* or impairment* or sequelae* or outcome* or effect* or result* or problem* or challenge* or impact* or late effect*) AND (crani* or brain*) AND (survivor* or young adult* or aya or adult) AND (adolescen* or teenage* or pediatric or paediatric or child* or childhood)*. Initial searches yielded a total of 789 results. Duplicates were removed, leaving a total of 691 records, and the remaining articles underwent a stepwise search strategy conducted at three levels, depicted in Figure 1. First, titles were screened to exclude review articles and studies clearly unrelated to review objectives. The abstracts of the remaining 445 papers were then reviewed and excluded according to the afore-mentioned criteria. Where it was not possible to determine inclusion from abstracts alone, studies progressed to the third stage of selection for more detailed review. In this stage, 90 records were reviewed in full against inclusion and exclusion criteria. The majority of studies were excluded due to irrelevant context, or because participants were younger than 16 years of age at the time of assessment, and/or because studies did not include participant subgroups or statistical analysis specific to the effects of CRT over other

types of treatments. Reference lists of these studies were also manually searched, and ten additional relevant publications were identified which were also read in full. A total of 21 studies met criteria for inclusion in the review (summarised in Tables 3 and 4).

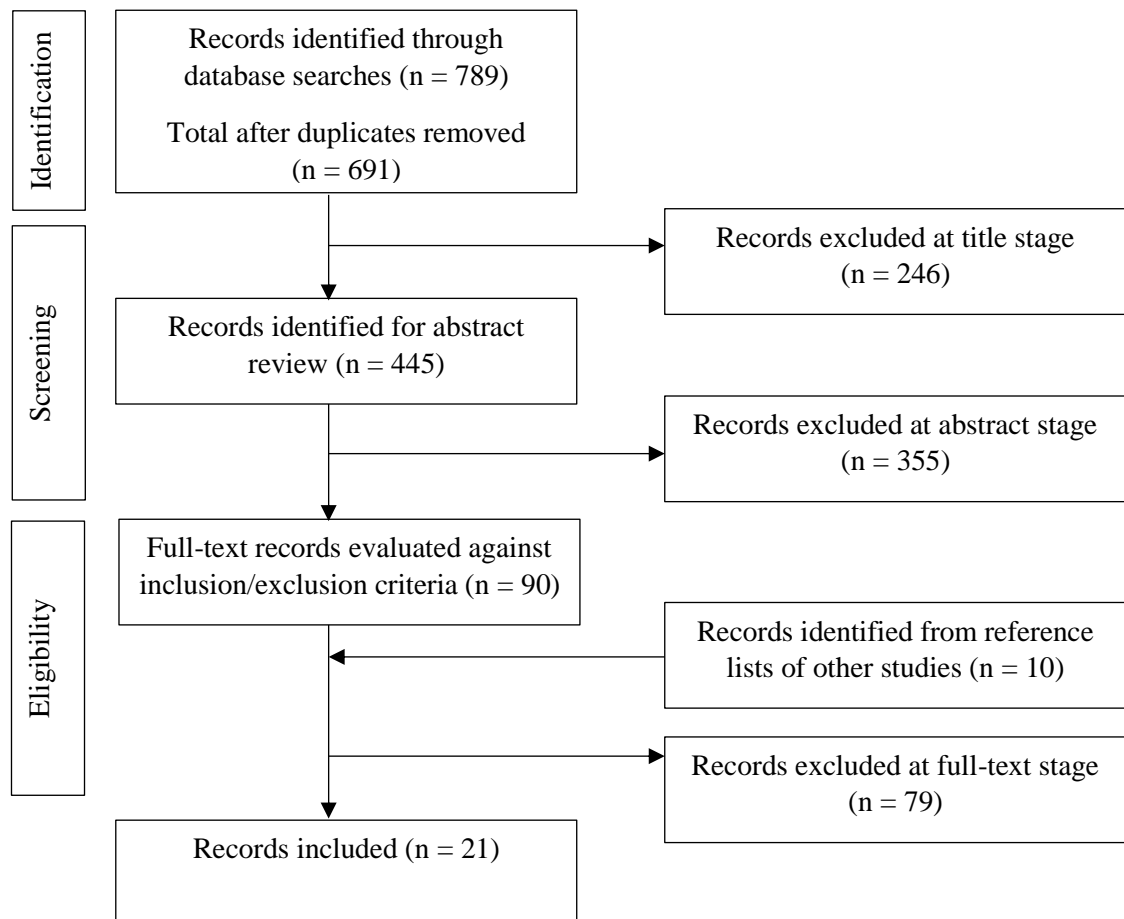


Figure 1. Flow chart of search results and screening process

Data extraction

The following information was abstracted for each study a) demographic information including mean age at diagnosis; mean age at evaluation; mean time since treatment b) study information including: year of publication; study location; design; whether it was part of a larger study; sample size; c) type of cancer studied, d) treatment

information including combination of treatments received and CRT dosage, d) outcomes information including: cognitive domains assessed; cognitive measures used; other outcome measures; statistical analysis used to differentiate effects of CRT, and e) findings relevant to the effects of CRT.

Categorisation of studies

Cancer type. Given that records were not selected based on specific types of cancer, studies were separated according to whether cancer originated in the central nervous system; eight studies focused on cancers originating in the central nervous system (CNS) summarised in Table 3, and thirteen studies focused on cancers not originating in the central nervous system (non-CNS), for which CRT is still a primary treatment, summarised in Table 4.

Six CNS studies contained mixed samples made up of participants with various brain tumours, commonly including medulloblastoma and astrocytoma. The remaining two CNS studies focused on pure samples of retinoblastoma and medulloblastoma patients, respectively (Brinkman et al., 2015; Maddrey et al., 2005). The majority of non-CNS studies comprised pure samples of acute lymphoblastic leukaemia (ALL) survivors. Of the remaining three, two contained mixed samples of ALL and other non-CNS cancers (Kadan-Lottick et al., 2010; Winqvist, Vainionpää, Kokkonen, & Lanning, 2001) and the third focused on a pure sample of participants who underwent treatment for non-Hodgkin lymphoma (Ehrhardt et al., 2018).

Table 1.

Methods of Differentiating Specific Effects of CRT across Studies

Study	
CNS Studies	
Ailion et al., 2016	No-CRT vs CRT
Armstrong et al., 2010	No-CRT vs different dosages of CRT
Brinkman et al., 2015	All participants - regression
Ellenberg et al., 2009	No-CRT vs different dosages of CRT
Jayakar et al., 2015	No-CRT vs CRT
King et al., 2017	No-CRT vs CRT
Maddrey et al., 2005	All participants - regression
Reimers et al., 2013	All participants - regression
Non-CNS Studies	
Armstrong et al., 2013	Dosage comparison
Daams et al., 2012	No-CRT vs CRT
Edelmann et al., 2014	No-CRT vs CRT
Ehrhardt et al., 2018	All participants - regression
Harila et al., 2009	No-CRT vs different dosages of CRT
Kadan-Lottick et al., 2010	No-CRT vs different dosages of CRT
Krull, Brinkman, et al., 2013	All participants - regression
Krull, Zhang, et al., 2013	No-CRT vs different dosages of CRT
Krull et al., 2014	Dosage comparison
Link et al., 2006	All participants - regression
Schuitema et al., 2013	No-CRT vs CRT
Schuitema et al., 2015	All participants - regression
Winqvist et al., 2001	No-CRT vs CRT

CRT. All studies included a subgroup of participants who had received CRT. However, according to the treatment protocols for many different types of cancer, most participants across all studies also received further treatment in addition to CRT, such as chemotherapy and/or surgery. Given that this review aims to evaluate the specific effects of CRT, only studies that included a method for differentiating the effects of CRT were included. The 21 studies were categorised accordingly (see Table 1); seven studies compared a CRT group to a no-CRT group, five studies

compared a no-CRT group to multiple groups who received different dosages of CRT, two studies compared two groups who received different dosages of CRT, and a further seven studies evaluated the association between CRT dose and impairment across all participants using regression analyses.

Characteristics of studies

Design. Across all CNS and non-CNS studies, the majority (90%) had a cross-sectional design, evaluating participants at a single interval. Only two longitudinal studies evaluated changes in survivors' cognitive abilities from active treatment to remission in adulthood (Harila et al., 2009; Krull, Zhang, et al., 2013); one of these studies also included further cross-sectional analysis (comparison to healthy controls) (Harila et al., 2009). The 21 studies were conducted in five different countries; the United States (n=14), the Netherlands (n=3), Finland (n=2), Sweden (n=1), and Denmark (n=1).

Participants. A total of nine studies recruited participants from existing cohort studies in the US; in six studies, participants were recruited from a cohort of over 1400 participants in the larger St. Jude Lifetime Cohort (SJLIFE) study (Brinkman et al., 2015; Edelmann et al., 2014; Ehrhardt et al., 2018; Krull, Brinkman, et al., 2013; Krull, Zhang, et al., 2013; Krull et al., 2014), which evaluates medical and psychosocial late effects in adult survivors of childhood cancer at St Jude Children's Research Hospital (Hudson et al., 2011). All participants in this cohort study were at least 18 years of age and ten years or more from diagnosis. Exclusion criteria included history of developmental disorder, neurologic event unrelated to cancer, and relapse. A further three studies (Armstrong et al., 2010;

Ellenberg et al., 2009; Kadan-Lottick et al., 2010) recruited eligible participants from the Childhood Cancer Survivor Study (CCSS), which is a large retrospective cohort study of children and adolescents with longitudinal follow up across 26 institutions in the US and Canada (Robison et al., 2002). All participants in this cohort study were diagnosed in childhood and had a survival rate of at least five years.

Sample size of treatment groups (excluding healthy controls) ranged from 16 to over 4000, but two thirds of the studies (67%) included between 25 and 135 participants who had received cancer treatment. Fourteen studies included additional healthy control groups and ten studies evaluated participants against population norms; three studies utilised both healthy controls and population norms (Armstrong et al., 2010; Edelmann et al., 2014; Ehrhardt et al., 2018). Most studies (90%) reported mean age at diagnosis, which ranged from 1.9 to 10.4. All studies reported mean age at evaluation, which was 28.8 years old on average, and ranged from 16.0 to 38.4. All except two studies reported mean time since treatment ended, which was 22 years on average, with a range of 9.7 to 33.5 years across CNS and non-CNS studies.

Measures. The neuropsychological tests used to assess cognitive functioning are detailed in Table 2. Seven studies (2 CNS, 5 non-CNS) also utilised structural neuroimaging including: structural magnetic resonance imaging (MRI) [n=5], functional magnetic resonance imaging (fMRI) [n=1], volumetric/atrophy analysis [n=3], diffusion-tensor imaging (DTI) [n=3], magnetoencephalography (MEG) [n=1], and fluorodeoxyglucose-positron emission tomography (F-FDG PET)[n=1], alongside measures of cognitive functioning.

Table 2.

Neurocognitive Measures used in Included Studies

Study	Intelligence	Memory	Attention	Processing Speed	General Executive Functions
CNS Studies					
Ailion et al., 2016				SDMT	
Armstrong et al., 2010		CCSS-NCQ	CCSS-NCQ		CCSS-NCQ
Brinkman et al., 2015	WASI	CVLT-II	CPT-II, TMTa, WAIS-III DSf	WAIS-III CD	TMTb, COWAT, WAIS-III DSf, BRIEF
Ellenberg et al., 2009		CCSS-NCQ	CCSS-NCQ		CCSS-NCQ
Jayakar et al., 2015	WASI	CVLT-II			
King et al., 2017	WASI	ACT	WMS DSf	OSDMT	
Maddrey et al., 2005	WAIS-III (2 subtests)	CVLT, Rey-O	CPT, TMTa		TMTb, COWAT, WCST
Reimers et al., 2013	WAIS-R				
Non-CNS Studies					
Armstrong et al., 2013	WASI (data NR)	WMS-IV, BCSE			
Daams et al., 2012		ANT	ANT	ANT	ANT
Edelmann et al., 2014	WASI	CVLT-II, WAIS-III DSf, TML-II	TMTa, CPT-II	GPT, PSI from WAIS-III	TMTb, COWAT, WAIS-III DSb

Ehrhardt et al., 2018	WASI	CVLT-II, WAIS-III DSf, TML-II	TMTa, CPT-II	GPT, PSI from WAIS-III	TMTb, COWAT, WAIS-III DSb, BRIEF
Harila et al., 2009	WAIS (7 subtests)	WMS, HIMT, VLT, BVRT	TMTa, TMTb, SCWT		
Kadan-Lottick et al., 2010		CCSS-NCQ	CCSS-NCQ		CCSS-NCQ
Krull, Brinkman, et al., 2013	WASI	CVLT-II	CPT-II, WAIS-III	PSI from WAIS-III	WAIS-III, Other test NR
Krull, Zhang, et al., 2013	WASI				
Krull et al., 2014	WASI	CVLT-II	CPT-II, WAIS-III, Other test NR	CPT-II, WAIS-III, Other test NR	WAIS-III, Other test NR
Link et al., 2006	WAIS-R (3 subtests), SRB Vocab	CMVMT	APT k-test	APT RT-2	AM, APT RT-Inhibition
Schuitema et al., 2013	WAIS-R (4 subtests)	ANT	ANT	ANT	
Schuitema et al., 2015	WAIS-III (4 subtests)	ANT	ANT	ANT	ANT
Winqvist et al., 2001	WAIS (6 subtests)	WMS DSf DSb, BVRT		TMTa, TMTb, SCWT, PPT, RRT, WAIS-III CD	TMTa, TMTb, BWT, SCWT

*ACT, Auditory Consonant Trigram 36s trial; AM, Austin Maze Test; ANT, Amsterdam Neuropsychological Tasks; APT RT-2, Automated Psychology Test System Reaction Time Test; APT RT-Inhibition, Automated Psychology Test Inhibition Test; BCSE, Brief Cognitive Status Exam; BRIEF, Behaviour Rating Inventory of Executive Function; BVRT, Benton Visual Retention Test; BWT, Bourdon-Wiersma Test; CCSS-NCQ, Childhood Cancer Survivor Study Neurocognitive Questionnaire; COWAT, Controlled Oral Word Association Test; CMVMT, Cronholm-Molander Verbal Memory Test; CPT, Conners' Continuous Performance Test; CPT-II, Conners' Continuous Performance Test-II; CVLT, California Verbal Learning Test; CVLT-II, California Verbal Learning Test-II; HIMT, Homogeneous Inference Memory Test; OSDMT, Oral Symbol Digit Modality Test; PSI, Processing Speed Index; Rey-O, Rey-Osterrieth Complex Figure Test; RTT, Reaction Time Test; SCWT, Stroop Colour Word Test; SDMT, Symbol Digit Modality Test; SRB Vocab, SRB 1 Vocabulary from the DS Battery; TMTa, Trail-making Test Part A; TMTb, Trail-making Test Part B; TML-II, Test of Memory and Learning-I; VLT, Verbal Learning Task; WAIS, Wechsler Adult Intelligence Scale; WAIS-III, Wechsler Adult Intelligence Scale-III; WAIS-III CD, Coding subtests; WAIS-III DSb, Digit Span backwards subtests; WAIS-III DSf, Digit Span forward subtests; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WASI, Wechsler Abbreviated Scale of Intelligence; WCST, Wisconsin Card Sorting Test; WMS, Wechsler Memory Scale; WMS-IV, Wechsler Memory Scale-IV; WMS DSf, Digit Span forwards subtests

Results

Information extracted from the studies in the present review will be synthesised and structured in the order of the research questions. It will first focus on the neurocognitive late effects of CRT, according to five domains across the 21 studies, separated for CNS and non-CNS cancer survivors (summarised in Table 5). Three risk factors (age at diagnosis, time since treatment, CRT dose) will also be evaluated (summarised in Table 6), and anatomical correlates of CRT considered.

Intelligence

The most widely used measures of intellectual functioning are the Wechsler scales, which purport to measure “the global capacity of a person to act purposefully, to think rationally, and to deal effectively with his environment” (Wechsler, 1958, p.7). Fifteen studies (5 CNS, 10 non-CNS) investigated the effects of CRT on IQ. The most frequently used measure was the Wechsler Abbreviated Scale of Intelligence (WASI), which is a shortened version of the full battery, yielding three index scores; full-scale IQ, verbal comprehension, and perceptual reasoning.

CNS studies

Of the five studies that examined IQ in CNS tumour survivors, two identified specific effects of CRT leading to impairment; CRT survivors were found to have significantly lower full scale IQ (in the low range; mean IQ=75-78.8) compared to chemotherapy survivors and controls (Maddrey et al., 2005; Reimers et al., 2003), with one suggesting stronger effects of CRT on perceptual reasoning over verbal comprehension (Maddrey et al., 2005; Reimers et al., 2003). A further two studies found a specific effect of CRT such that those who received CRT achieved lower IQ

scores than those treated with other modalities and controls, but IQ remained within the average range (Jayakar, King, Morris, & Na, 2015; King, Ailion, Fox, & Hufstetler, 2017). The remaining study did not find any association between CRT and IQ (Brinkman et al., 2015).

Non-CNS studies

Only one non-CNS study suggested that CRT may impair aspects of intellectual functioning; Krull et al., (2014) found that scores on a vocabulary subtest in a small sample of 38 ALL survivors were significantly lower than population norms for even low doses of CRT.

Seven studies did not suggest any effect of CRT on intelligence above other treatments. Five of these studies compared an overall non-CNS survivors group (CRT and other treatments included) to controls or population norms and found that survivors had lower IQs than controls, but were still within the average range (Ehrhardt et al., 2018; Krull, Zhang, et al., 2013; Link et al., 2006; Schuitema et al., 2015; Winqvist et al., 2001). Three of these studies included further analysis yet failed to detect independent effects of CRT on IQ for ALL, non-Hodgkin's lymphoma, and mixed non-CNS tumours. When subgroups of ALL survivors who received CRT and chemotherapy, chemotherapy only, and controls were compared, IQ was significantly poorer in the CRT group than controls but not statistically different to the chemotherapy group, suggesting no distinct effect of CRT (Edelmann et al., 2014; Schuitema et al., 2013).

A further two studies found that CRT survivors had significantly poorer scores than controls and other treatment groups but scores remained within the average range

(Harila et al., 2009; Krull, Brinkman et al., 2013). Of note, Harila et al.'s (2009) longitudinal data revealed decline in verbal comprehension index points for both CRT (7 points) and no-CRT (8 points) subgroups, and perceptual reasoning decline only for the CRT group (12 points) from first assessment to five years post-treatment. Moreover, verbal comprehension and perceptual reasoning scores in the CRT subgroup continued to decline from five to 20 years post-treatment, whilst the no-CRT group scores did not. However, in a similar longitudinal study, Krull, Zhang et al. (2013) reported that, despite their overall finding that survivors treated with CRT experienced initial declines in perceptual reasoning followed by later declines in verbal comprehension, this was not the case for 48% of survivors who did not demonstrate any significant decline in verbal comprehension over time.

Conclusions

Only studies of childhood CNS cancers which differentiated the effects of CRT suggested intellectual impairment up to 34 years later, particularly in perceptual reasoning. Most other studies indicated that, even if a differential effect of CRT was found, IQ was not impaired relative to controls or population norms. However longitudinal data suggest that these survivors may still have experienced significant declines above those of survivors who did not receive CRT. It is also important to note that most studies used estimates of IQ based on limited subtests, and only one study (Reimers et al., 2003) calculated an estimate of full scale IQ based on subtests also assessing working memory and processing speed. Given that these cognitive functions are proposed to be significantly affected by CRT, it is possible that all other included studies overestimated full scale IQ. Further research using full version of the Wechsler scales is required to account for this interaction, and further elucidate the effects of CRT on overall intellectual functioning.

Table 3.

Overview of CNS Cancer Studies

Study	Design, Country	Cancer type	Comparative groups	Treatment sample (percentage of sample receiving CRT)	Dosage (SD)	Mean/ median age at diagnosis (SD) Range	Mean/ median age at evaluation (SD) Range	Mean/ median time since treatment (SD) Range	Domains assessed Other measures	Relevant findings
Ailion et al., 2016	Cross-sectional US	13 medulloblastoma 10 astrocytoma 1 ependymoma 1 pineoblastoma	25 matched healthy controls	14 CRT + chemotherapy 10 surgery only 1 chemotherapy only 25 total (56%)	NR	9.3 (5.1) 1-19	23.7 (5.1) 18-35	15.0 (5.0) NR	Processing speed MRI, atrophy, lesion size, social status	<ul style="list-style-type: none"> Adult survivors of paediatric cerebellar tumours diagnosed at a young age and treated with CRT displayed the highest amount of cerebellar atrophy Greater cerebellar atrophy was associated with poorer oral and written processing speed for individuals with smaller lesion sizes
Armstrong et al., 2010	Cross-sectional US	523 astrocytoma 169 medulloblastoma 126 other CNS tumour	Sibling group Population norms	CCSS 333 CRT + surgery 164 CRT + surgery + chemotherapy 271 surgery only 50 other 818 total (63.6%)	Radiation dosimetry method used Ranges: 0-30Gy 30-50Gy >50Gy	NR NR 0-20	31.3 (7.0) 18.3-51.8	>5 years NR NR	Memory, attention, executive functioning Health-related Quality of Life	<ul style="list-style-type: none"> CRT to the temporal region (but not other regions) was significant associated with memory problems and poor task efficiency. Dose-response effect of CRT dose in memory problems and poor task efficiency

Brinkman et al., 2015	Cross-sectional US	Retinoblastoma	Population norms	SJLIFE 6 CRT only 26 surgery only 6 CRT + surgery 3 CRT + chemotherapy 13 surgery + chemotherapy 15 CRT + chemotherapy + surgery 69 total (43%)	Mean brain dose 26.3Gy (18.8)	1.9 (1.7) 0.0-7.1	32.5 (6.7) 20.5 - 46.2	30.6 (6.6) 17.2-45.5	Intelligence, memory, attention, executive functioning, processing speed Questionnaire data including demographics and history	<ul style="list-style-type: none"> Survivors diagnosed at <1 year of age performed significantly better on measures of verbal memory, verbal learning, and verbal reasoning abilities Increased whole brain radiation exposure was associated with poorer performance on verbal memory tasks, after adjusting for age at diagnosis
Ellenberg et al., 2009	Cross-sectional US	495 astrocytoma 172 medulloblastoma 135 other CNS tumour	5870 survivors of non-CNS cancers 382 sibling controls	CCSS 13 CRT only 225 surgery only 3 CRT + chemotherapy 12 chemotherapy + surgery 344 CRT + surgery 150 CRT + chemotherapy + surgery 802 total (63.6%)	62% irradiated CNS survivors received >40 Gy 92% irradiated non-CNS survivors received <40Gy	NR NR 0 - 20	31.5 (7.1) 17.4 - 51.8	NR NR 16.1-34.6	Memory, attention, executive functioning	<ul style="list-style-type: none"> CNS malignancy survivors reported significantly greater neurocognitive dysfunction than the sibling cohort or non-CNS malignancy survivors For CNS survivors, CRT was correlated with greater impairment on Task Efficiency and Memory Dose-response effect of CRT
Jayakar et al., 2015	Cross-sectional US	10 astrocytoma 9 medulloblastoma 5 craniopharyngioma 3 ganglioglioma 8 other CNS tumours	59 matched healthy controls	CRT group: (5 CRT only 11 CRT + chemotherapy) No-CRT group: (1 chemotherapy, 18 treatments NR) 35 total (46%)	Mean dose in CRT group 54.1 Gy (1.35) Range 50-55.8Gy	8.2 (5.3) 1-17	24.1 (4.9) 17-36	15.4 (5.3) 5-24	Intelligence, memory MRI, Brain volume, hippocampus volume, putamen volume	<ul style="list-style-type: none"> The volumes for subcortical structures (hippocampus and putamen) of the no-CRT group were similar to those of controls and smaller for the CRT group. Whole brain volumes of CRT and no-CRT groups are similar, but significantly smaller than controls

King et al., 2017	Cross-sectional US	19 astrocytoma 18 embryonal tumour 4 craniopharyngioma 3 ganglioglioma 3 ependymoma 3 glioma 8 other tumour	57 matched healthy controls	10 CRT only 1 chemotherapy only 17 CRT + chemotherapy 29 No CRT (treatment NR) 57 total (47%)	NR - coded as dichotomous variable (RT vs no RT)	7.8 (4.6) 1-17	24.2 (4.9) 18-35	16.5 (6.6) 5-30	Intelligence, memory, attention, processing speed Medical records, SES	<ul style="list-style-type: none"> • Within CRT survivors, a greater number of individuals exhibited impairment across all measures relative to the no-CRT group and controls • Younger age at diagnosis and CRT resulted in lower processing speed
Maddrey et al., 2005	Cross-sectional US	16 medulloblastoma	Population norms	7 CRT only 9 CRT + chemotherapy 8 and 10 participants had surgery and VP shunt placements, respectively 16 total (100%)	BED used - Across RT group mean dose 37.9Gy with 15.5 Gy posterior fossa boost (mean total dose 53.4 Gy)	7.3 (4.5) NR	21.9 (3.6) NR	14.6 (3.5) NR	Intelligence, memory, attention, executive functioning Quality of life, psychological distress	<ul style="list-style-type: none"> • Younger age at diagnosis was associated with greater executive function impairment, and greater time since diagnosis were related to deficits in verbal memory. • No significant associations between current age, CRT dose, use of chemotherapy, VP shunt placement, and level of neuropsychological impairment.
Reimers et al., 2003	Cross-sectional Denmark	24 medulloblastoma 71 astrocytoma 8 ependymoma 9 glioma 4 craniopharyngioma 8 germ cell 9 other CNS tumour	Population norms	55 surgery only 4 CRT only 44 CRT + surgery 2 chemotherapy + surgery 28 CRT + chemotherapy + surgery 133 total (57%)	28 whole brain, mean 35Gy plus 19Gy boost to tumour 19 whole brain only, mean 54Gy 29 focal, mean 51Gy	8.2 (3.8) 0-14.9	21.1 (7.9) NR	13.3 (7.3) 2-27.9	Intelligence Rappaport Disability Rating Scale Form	<ul style="list-style-type: none"> • Effects of CRT was stronger on performance IQ than verbal IQ; higher performance than verbal IQ was only observed in the non-irradiated group • CRT was the biggest risk factor for impaired cognitive outcome. Younger age at diagnosis, tumour site in the cerebral hemisphere and hydrocephalus were also risk factors. Results were not significantly affected by whole brain vs focal CRT

*BED, biologically effective dose; CCSS, Childhood Cancer Survivor Study; DTI, diffusion tensor imaging; NR, not recorded; MRI, magnetic resonance imaging; SES, socioeconomic status; SJLIFE, St Jude Lifetime Cohort Study;

Table 4.

Overview of Non-CNS Cancer Studies

Study	Design, Country	Cancer type	Comparative groups	Treatment sample (percentage of sample receiving CRT)	Dosage (SD)	Mean/ median age at diagnosis (SD) Range	Mean/ median age at evaluation (SD) Range	Mean/ median time since treatment (SD) Range	Domains assessed Other measures	Relevant findings
Armstrong et al., 2013	Cross- sectional US	ALL	Population norms	265 CRT + chemotherapy 265 total (100%)	127: 18Gy 138: 24Gy	6.9 (4.0) NR	37.1 (6.6) NR	29.1 (6.6) NR	Intelligence, memory MRI with DTI, medical assessment, questionnaire data	<ul style="list-style-type: none"> Survivors who received 18 Gy CRT had no statistically significant impairment in immediate or delayed memory. Those who received 24 Gy showed twice the rate of impairment. Memory impairment was related to brain imaging
Daams et al., 2012	Cross- sectional Netherlands	ALL	35 healthy controls	18 chemotherapy only 14 CRT + chemotherapy 32 total (43.7%)	25Gy	5.7 (3.4) NR	31.0 (4.3) NR	25.3 (2.5) NR	Memory, attention, executive functioning, processing speed MEG	<ul style="list-style-type: none"> The chemotherapy + CRT group performed worse than controls on measures of cognitive flexibility, attentional fluctuations during sustained attention, visuomotor accuracy and sequential visuospatial working memory Findings suggest that the irradiated brain might be ageing faster and could be at risk for early-onset dementia. The chemotherapy group showed no signs of early ageing.

Edelmann et al., 2014	Cross-sectional US	ALL	Population norms 23 healthy controls	SJLIFE 36 chemotherapy only 39 CRT (other treatment NR) 75 (52%)	Mean dose 20Gy (5.7)	2.8 (1.7) NR	26.7 (3.4) NR	23.9 (3.1) NR	Intelligence, memory, attention, executive functioning, processing speed MRI with DTI	<ul style="list-style-type: none"> • The chemotherapy-only group performed better than survivors treated with CRT in only 3 of 20 neurocognitive measures (verbal selective reminding, memory span, visual-motor processing speed). • All survivors showed reduced white and grey matter brain fraction when compared with controls
Ehrhardt et al., 2018	Cross-sectional US	Non-Hodgkin Lymphoma	Population norms 181 community controls	SJLIFE 43 (23%) CRT (+ other treatments NR) 187 total (23%)	NR - coded as dichotomous variable (RT vs no RT)	10.4 (NR) 1.8-20.8	35.7 (8.9) 19.3-58.3	25.5 (NR) 10.5-47.7	Intelligence, memory, attention, executive functioning, processing speed Emotional distress, health-related quality of life	<ul style="list-style-type: none"> • Survivors' intelligence and attention were within normal limits; however, memory, executive function, and processing speed were impaired in comparison with both population norms and community controls • Treatment type, including CRT, was not significantly associated with neurocognitive performance
Harila et al., 2009	Cross-sectional Longitudinal Finland	ALL	45 healthy controls	20 chemotherapy only 44 CRT + chemotherapy	16: 18-23Gy 22: 24-25Gy 6: 30-48Gy	5.0 (NR) 0.8-15	26.0 (NR) 16-37	20.0 (NR) 10-32	Intelligence, memory, attention	<ul style="list-style-type: none"> • CRT survivors achieved lower scores across verbal and performance IQ, memory functions, and attention compared to the non-irradiated group and controls. Non-irradiated survivors performed significantly better, but also demonstrated had significant impairments in some domains. • Significant decline during the study period was observed both in VIQ and PIQ in the irradiated group, but only in VIQ in the non-irradiated group

Kadan-Lottick et al., 2010	Cross-sectional US	1939 ALL 908 Hodgkin disease 509 Non-Hodgkin lymphoma 613 Soft tissue sarcoma tumours 649 Wilms tumour 1319 other non-CNS cancers	382 healthy siblings	CCSS 452 CRT only 1663 chemotherapy only 3178 CRT + chemotherapy 284 No CRT or chemotherapy 5937 total (61%)	Coded as No CRT, 0.1-18Gy, >18Gy	8.5 (6.0) 0.0-20.0	32.2 (7.6) 17.0-54.1	23.7 (4.5) 16.0-34.3	Memory, attention, executive functioning Emotional distress	<ul style="list-style-type: none"> • Mean test scores of non-CNS cancer survivors varied only slightly (<0.5 SD) or not at all from the sibling group. Patient groups at highest risk were those with ALL but only if they also received CRT. • Chemotherapy was not statistically significantly associated with self-reported neurocognitive functioning after adjusting for age, sex, and CRT • There was no additional risk of impairment after 24Gy of CRT compared to under 24Gy
Krull, Brinkman, et al., 2013	Cross-sectional US	ALL	Population norms	SJLIFE 214 chemotherapy only 353 CRT (other treatment NR) 567 total (62%)	167: 18Gy 186: 24Gy	6.3 (4.3) NR	33.0 (NR) NR	26.0 (NR) NR	Intelligence, memory, attention, executive functioning Medical records	<ul style="list-style-type: none"> • Compared with the no CRT group, 24Gy CRT group showed increased risk for impairment in intelligence and memory, dependent on age at diagnosis. Age at diagnosis influenced impact of CRT • Mild impairments were also demonstrated in 18Gy only and chemotherapy only groups, particularly in flexibility, fluency, and working memory • Impairment in executive functioning increased with time since diagnosis for 24Gy CRT group.

Krull, Zhang, et al., 2013	Longitudinal US	ALL	Population norms	SJLIFE 102 CRT + chemotherapy 102 total (100%)	34: 18Gy 68: 24Gy	5.0 (3.2) 0.8-15.3	38.5 (6.2) 26.6-54.7	33.5 (5.7) 18.8-46.4	Intelligence, memory, attention, executive functioning, processing speed Medical records	<ul style="list-style-type: none"> • Results suggested an initial decline in performance IQ after CRT, followed by late decline in verbal IQ over a follow-up period of median 28.5 years later, suggesting a progressive effect on brain function from CRT • Decline in verbal IQ was associated with current attention and reading problems, in contrast to variables associated with early decline in abilities (such as CRT dose, age at exposure, and gender)
Krull et al., 2014	Cross-sectional US	ALL	Population norms	SJLIFE 38 CRT (other treatment NR) 38 (100%)	19: 18Gy 19: 24Gy	2.9 (1.6) NR	27.5 (3.5) NR	24.5 (3.0) NR	Intelligence, memory, attention, executive functioning, processing speed F-FDG PET imaging, medical records	<ul style="list-style-type: none"> • Both 18Gy and 24Gy CRT groups demonstrated significant impairment on measures of vocabulary, reading, mathematics, oral naming speed, working memory, attention span, and cognitive flexibility. No differences were apparent between groups. • Decreased efficiency of the frontostriatal brain circuit suggested, particularly for those treated with 24Gy

Link et al., 2006	Cross-sectional Sweden	ALL	44 matched healthy controls	44 CRT + chemotherapy 44 (100%)	Mean dose 24Gy (18-30)	4 (NR) 1-17	24.8 (NR) 19.8-31.3	20 (NR) NR	Intelligence, memory, executive functioning, processing speed Quality of life, social support, school education, questionnaire data	<ul style="list-style-type: none"> • Compared to controls, ALL survivors had significantly lower scores in tests of vocabulary and general knowledge, spatial ability, memory and learning, and perceptual and psychomotor speed. • Younger age at CRT treatment was associated with poorer cognitive outcomes. Survivors treated before the age of 6 showed significantly lower scores, but there was wide variation within this group • Cognitive outcomes were not significantly affected by CRT dose or time since treatment
Schuitema et al., 2013	Cross-sectional Netherlands	ALL	49 healthy controls	49 chemotherapy only 44 CRT + chemotherapy	Mean dose 22.5Gy (6.9)	5.7 (3.7) NR	31.2 (4.8) NR	25.4 (3.2) NR	Intelligence, memory, attention, executive functioning, processing speed MRI with DTI	<ul style="list-style-type: none"> • CRT survivors demonstrated significantly decreased fractional anisotropy (FA) compared with controls in frontal, parietal, and temporal white matter (WM) tracts. Decreases in FA correlated well with neuropsychological dysfunction. • Younger age at CRT and higher dosage were associated with worse WM integrity. • Accelerated ageing of the brain and increased risk of early onset dementia are suspected after CRT, but not after chemotherapy.

Schuitema et al., 2015	Cross-sectional Netherlands	ALL	58 healthy controls	50 CRT + chemotherapy 50 total (100%)	Mean dose 22.5Gy (6.8)	5.6 (3.8) NR	31.1 (4.9) NR	25.5 (3.1) NR	Intelligence, memory, attention, executive functioning	<ul style="list-style-type: none"> Survivors showed impaired working memory capacity, inhibition, cognitive flexibility, visuomotor control, attentional fluctuations, and sustained attention. Younger age at diagnosis and older age at assessment were associated with worse cognitive performance Female gender and higher dose CRT were additional risk factors. There was no indication of dose effects of chemotherapy across cognitive tasks.
Winqvist et al., 2001	Cross-sectional Finland	19 ALL 2 Morbus Hodgkin's 6 other non-CNS tumours	22 healthy controls	18 CRT (other treatment NR) 9 No CRT (other treatments NR) 27 total (67%)	Mean dose 29.7Gy (9.8)	8.6 (5.1) 1.2-15.4	18.7 (3.0) 16.0-28.6	9.7 (5.2) 3.0-19.5	Intelligence, memory, attention	<ul style="list-style-type: none"> Though cancer survivors obtained lower test scores in intelligence, memory, and some motor function tests compared to controls, the cancer survivors' IQ scores were not defective but reached a normal average level. CRT survivors showed more difficulty on short-term memory tests that demand special attention, the reaction time test, and Digit Span subtest of the WAIS, compared to non-irradiated survivors and controls.

*BED, biologically effective dose; CCSS, Childhood Cancer Survivor Study; DTI, diffusion tensor imaging; MRI, magnetic resonance imaging NR, not recorded; PIQ, performance IQ; SJLIFE, St Jude Lifetime Cohort Study; VIQ, verbal IQ

Memory

Memory is the term given to the processes involved in the encoding, storage, and subsequent retrieval of information. Memory measures typically assess episodic (memory for events) and/or working memory (ability to hold in mind and mentally manipulate information over short periods of time). The most commonly used measure in the included studies was the California Verbal Learning Test, second edition (CVLT-II). Eighteen studies (5 CNS, 12 non-CNS, 1 both) examined the impact of CRT on memory.

CNS studies

Armstrong et al. (2010) showed that CRT to the temporal region, but not other regions, was associated with increased risk for memory difficulties on a self-report measure. On behavioural tests, CRT was found to be associated with poorer short-term and long-term verbal memory in a sample of retinoblastoma survivors relative to population norms (Brinkman et al., 2015). Working memory was also found to be poorer in brain tumour survivors compared to healthy controls, although working memory was also impaired to a lesser extent in the no-CRT group, suggesting the presence of other factors affecting memory (King et al., 2017). A further two studies concluded that there was an overall effect of both CRT and chemotherapy, particularly on encoding ability, but additional analyses revealed no independent effect of CRT (Jayakar et al., 2015; Maddrey et al., 2005).

Table 5.

Summary of the Effects of CRT across Neurocognitive Domains

	Neurocognitive domains				
	Intellect	Memory	Attention	Processing Speed	Executive Functions
CNS Studies					
Ailion et al., 2016				◆	
Armstrong et al., 2010		◆	◆		◇
Brinkman et al., 2015	◇	◆	◇	◇	◇
Ellenberg et al., 2009		◆	◆		◇
Jayakar et al., 2015	+	◇			
King et al., 2017	+	◆	◆	◆	
Maddrey et al., 2005	◆	◇	◇		◇
Reimers et al., 2003	◆				
Non-CNS Studies					
Armstrong et al., 2013		◆			
Daams et al., 2012		◆	◆	◇	◆
Edelmann et al., 2014	◇	◆	◇	◆	◇
Ehrhardt et al., 2018	◇	◇	-	◇	◇
Harila et al., 2009	+	◆			◆
Kadan-Lottick et al., 2010		◆	◆		◆
Krull, Brinkman, et al., 2013	+	◆	◇	◆	◇
Krull, Zhang, et al., 2013	◇				
Krull et al., 2014	◆	-	◆	-	-
Link et al., 2006	◇	-	-	-	◇
Schuitema et al., 2013	◇	◆	◆	◆	
Schuitema et al., 2015	-	-	◆	-	-
Winqvist et al., 2010	◇	◆		◆	◇

◆ = Significant effect of CRT, ◇ = No significant effect of CRT above other treatments, '+' = Significant effect of CRT but no impairment, '-' = Studies did not differentiate specific effects of CRT

Non-CNS studies

Of the 12 studies examining the effects of CRT on memory, five concluded that irradiation had adverse effects beyond those of other treatments, with impairment demonstrated in: verbal memory and memory interference (Harila et al., 2009); verbal and visual delayed memory (Armstrong et al., 2013); learning, short-term and long-term recall, and working memory (Krull, Brinkman, et al., 2013); visuospatial working memory (Schuitema et al., 2013); and self-reported memory functioning (Kadan-Lottick et al., 2010). Of note, Armstrong et al. (2013) and Krull, Brinkman,

et al. (2013) only reported impairment after 24Gy CRT (not 18Gy) suggesting an interaction with dosage.

Memory impairment was also observed in mixed samples where participants received both CRT and chemotherapy, relative to controls (Krull et al., 2014; Link et al., 2006; Schuitema et al., 2015). A further three studies identified unique effects of CRT on select memory functions in their analysis; in these studies, participants treated with CRT and chemotherapy were compared to chemotherapy-only subgroups and were found to show poorer scores on measures of sequential working memory (Daams et al., 2012), verbal selective reminding, and memory span (Edelmann et al., 2014). When examining the differences, Winqvist and colleagues (2001) noted that CRT survivors tended to perform more poorly than the no-CRT group on more difficult memory tests.

Only one study did not identify CRT as a risk factor for impaired memory in regression analysis, despite significant differences between the overall survivor group and controls (Ehrhardt et al., 2018).

Conclusions

In a study examining both CNS and non-CNS cancer survivors, there were no differences between CNS and non-CNS survivors who received CRT, and both subgroups showed greater impairments than participants who did not receive CRT (Ellenberg et al., 2009). Overall, the included studies suggest that memory and working memory are similarly affected in adult survivors of different cancer types treated with CRT, and may be consistent with the early onset of cognitive ageing.

Armstrong and colleagues (2013) even concluded that memory function in their sample of ALL survivors was equivalent to an adult older than 69 years in the general population.

It is also proposed that the effects of CRT on memory performance interact with other factors such CRT dosage, location in the brain, and other concurrent treatments. Many studies suggest that chemotherapy also has specific adverse effects on memory, although the impact of CRT appears to still surpass that of chemotherapy alone, especially on more complex memory tasks (which may require other cognitive skills also affected by CRT).

Attention

Attention can be conceptualised as a limited-capacity process that allows the preferential processing of certain sensory information at the expense of other available stimuli. Attention is crucial as it influences the efficiency of other functions and modulates many other areas of cognition. Fourteen studies (4 CNS, 9 non-CNS, 1 both) investigated the effects of CRT on aspects of attention.

CNS studies

All four CNS studies included statistical analysis to differentiate the effects of CRT on attention. Two studies concluded that CRT had adverse effects on attention by comparing CRT and no-CRT subgroups, although these conclusions are limited as King et al. (2017) used only a digit span forwards task and Armstrong et al. (2010) used a self-report measure of task efficiency to measure attention. Two further studies which used a validated continuous performance task (CPT) found no

association between CRT and performance (Brinkman et al., 2015; Maddrey et al., 2005).

Non-CNS studies

Of the nine non-CNS studies, five studies demonstrated some independent effects of CRT on attention (Daams et al., 2012; Kadan-Lottick et al., 2010; Krull et al., 2014, Schuitema et al., 2013; Schuitema et al., 2015), although two of these found only selective effects on attention span (Krull et al., 2014) and attentional fluctuations during a sustained attention task (Daams et al., 2012). A further two studies suggested that CRT and chemotherapy equally impair attention relative to controls (Edelmann et al., 2014; Krull, Brinkman, et al., 2013), although this was limited to measures of attention variability for Edelmann et al., (2014), with no significant effects of either treatment on sustained or focused attention. The remaining two studies, which did not analyse CRT and chemotherapy separately, concluded that attention was within normal limits in non-CNS survivors (Ehrhardt et al., 2018; Link et al., 2006).

Conclusions

Ellenberg et al. (2009) examined both CNS and non-CNS survivors from the Childhood Cancer Survivor Study. They concluded that, although CRT impacts all cancer survivors, it has greater effects in survivors of CNS cancers; they found that CNS CRT survivors reported greater task efficiency impairment than the non-CNS CRT survivors, who in turn reported greater impairment than survivors who did not receive CRT. In contrast, no strong patterns are present in the results of the included CNS studies. The mixed results may somewhat be explained by the variety of attention tasks measuring different aspects of attention.

Processing Speed

Processing speed is typically conceptualised as the rate at which a person can complete mental operations. Twelve studies (3 CNS, 9 non-CNS) investigated the effects of CRT on processing speed.

CNS studies

Of the three studies that examined adult survivors of childhood brain tumours, two concluded that CRT had an adverse effect on processing speed (Ailion et al., 2016; King et al., 2017). The remaining study failed to find any effect (Brinkman et al., 2015). All three studies employed statistical analysis to differentiate specific effects of CRT, although King et al. (2017) reported effect sizes only.

Non-CNS studies

Of the nine studies that examined the effects of CRT on processing speed in non-CNS cancers, three indicated some independent adverse effect of CRT; two of these studies compared subgroups of participants receiving CRT and chemotherapy, chemotherapy only, and healthy controls, and concluded that processing speed was significantly slower for the CRT subgroup (Edelmann et al., 2014; Schuitema et al., 2013). The other compared irradiated and non-irradiated participants and found a significant difference in performance on the digit symbol coding subtest of the WAIS (Winqvist et al., 2001). A further three studies suggested that processing speed is impaired by treatment with both CRT and chemotherapy but did not differentiate treatment type (Krull et al., 2014; Link et al., 2006; Schuitema et al., 2015).

The remaining three studies failed to identify any specific effects of CRT on processing speed. Daams et al. (2012) found no significant differences between

participants treated with CRT and chemotherapy, with chemotherapy only, and controls, although the measure they used was primarily validated as a measure of executive function. The other two studies included CRT as a factor in regression analyses exploring risk factors associated with processing speed; although Ehrhardt et al. (2018) did not identify any significant association, Krull, Brinkman, et al. (2013) propose gender as an equal and interacting risk factor, as their findings suggested that processing speed was only affected in female participants who had received at least 24Gy CRT.

Conclusions

Taking CNS and non-CNS studies together, it seems that processing speed is vulnerable to the effects of cancer treatment in childhood, and the impact mostly endures to adulthood. Slowed processing speed is observed across studies where participants have had CRT and chemotherapy, and CRT alone, especially on visual-motor tasks but also on pure tasks of processing speed which do not depend on motor functioning. Additional factors such as gender and chemotherapy are suggested, however, two studies with effective designs that included a chemotherapy-only group (therefore providing the best evidence for some independent effect of CRT) indicated that performance remains significantly poorer in participants who received CRT.

General Executive Functions

General executive functions encompass aspects of global executive functioning that are separate from the central components of attention, working memory, and processing speed. Various measures of cognitive flexibility, fluency, inhibition, and self-reported emotional regulation and organisation were used across the fourteen

studies (4 CNS, 10 non-CNS) that examined the impact of CRT on executive functions.

CNS studies

Three CNS studies found that their overall survivor sample was impaired relative to norms on measures of cognitive fluency (Brinkman et al., 2015), verbal fluency and set-shifting (Maddrey et al., 2005), and self-reported organisation and emotion regulation (Ellenberg et al., 2009), but additional analyses revealed no specific effects of CRT. Armstrong et al. (2013) used the same self-report measure, and found no significant association between CRT to any brain region and emotional regulation or organisation.

Non-CNS studies

Whilst three studies found that cognitive fluency, flexibility and inhibition were poorer in a broad group of participants who received CRT and chemotherapy compared to controls (Krull et al., 2014; Link et al., 2006; Schuitema et al., 2015), they did not include analysis to differentiate the effects of CRT and chemotherapy. Of the seven non-CNS studies that did, three concluded that CRT had specific adverse effects on accuracy of set-shifting (Daams et al., 2012), inhibition and visual attention (Harila et al., 2009), and self-reported organisation but not emotion regulation (Kadan-Lottick et al., 2010). The remaining four studies did not identify any impact of CRT exceeding that of chemotherapy (Edelmann et al., 2014; Ehrhardt et al., 2018; Krull, Brinkman, et al., 2013; Winqvist et al., 2001). However, Krull, Brinkman, et al. (2013) suggested that survivors treated with a higher CRT dosage (24Gy) were at greater risk for executive functioning impairment with increasing

years from diagnosis, such that the risk was six times greater 45 years after treatment compared to the no-CRT group.

Conclusions

There was no specific impact of CRT on general executive functions in CNS studies. Non-CNS studies suggested some increased difficulty with set-shifting and inhibition related to CRT but it is difficult to distinguish the effects of different treatments on performance. Executive functioning may also be increasingly vulnerable over time for survivors who received CRT. However, it is important to consider other factors, for example two studies found that general executive functions were equally or more strongly affected by emotional distress than CRT (Ehrhardt et al., 2018; Kadan-Lottick et al., 2010).

Other Risk Factors

The present review also sought to answer whether cognitive outcomes are related to age at diagnosis, time since treatment, and CRT dosage. Results are summarised in Table 6.

Age at diagnosis

Fifteen (7 CNS, 8 non-CNS) of 21 studies examined the effects of age at diagnosis on cognitive functioning in adulthood.

CNS studies

The two CNS studies that investigated the interaction between CRT and age at diagnosis indicated that, among participants who had received CRT only, an earlier age of diagnosis was associated with poorer performance on measures of processing

speed (Ailion et al., 2016) and working memory (King et al., 2017).

Table 6.

Summary of Effects of Risk Factors

	Risk Factors		
	Age at Diagnosis	Time since treatment	CRT Dosage
CNS Studies			
Ailion et al., 2016	◆		
Armstrong et al., 2010	◇		◆
Brinkman et al., 2015	◆		
Ellenberg et al., 2009	◇	◇	◆
Jayakar et al., 2015			
King et al., 2017	◆		
Maddrey et al., 2005	◆	◆	◇
Reimers et al., 2003	◆	◇	◆
Non-CNS Studies			
Armstrong et al., 2013	◇	◇	◆
Daams et al., 2012			
Edelmann et al., 2014			
Ehrhardt et al., 2018			
Harila et al., 2009			◇
Kadan-Lottick et al., 2010	◆	◆	◆
Krull, Brinkman, et al., 2013	◆	◆	◆
Krull, Zhang, et al., 2013	◇	◇	◇
Krull et al., 2014			◇
Link et al., 2006	◆	◇	◇
Schuitema et al., 2013	◆	◆	◇
Schuitema et al., 2015	◆	◆	◆
Winqvist et al., 2001	◆		

◆ = Significant effect, ◇ = No significant effect

Although a further three studies suggested that age at diagnosis had significant effects on memory (Brinkman et al., 2015), executive functioning (Maddrey et al., 2005), and IQ (Reimers et al., 2003), they did not control for CRT as a risk factor in their analyses. Reimers et al.'s (2003) separate linear regression models instead proposed that CRT and age at diagnosis, in addition to shunt and tumour location, constitute four “approximately additive” factors (p. 33). Of note, Brinkman et al.'s (2015) findings in retinoblastoma survivors were in contrast with the broader cancer

survivor literature as they indicated that diagnosis before 1 year of age was related to better neuropsychological performance. However, the other two studies found correlations such that younger age at diagnosis was related to greater cognitive impairment in adulthood. A further two studies measured self-reported neurocognitive functioning and found no significant association with age at diagnosis (Armstrong et al., 2010; Ellenberg et al., 2009).

Non-CNS studies

Of the eight non-CNS studies, only two failed to find any effect of age at diagnosis. In these studies, regression analyses did not find any association between age at diagnosis, CRT dose, and memory deficits (Armstrong et al., 2013) or decline in verbal IQ (Krull, Zhang, et al., 2013). The other six studies concluded that younger age at diagnosis was related to greater impairment in cognitive functioning in adulthood, largely affecting IQ, memory, and motor/visuomotor functioning, although only three examined the effects of age at diagnosis in participants who received CRT in particular (Krull, Brinkman, et al., 2013; Link et al., 2006; Schuitema et al., 2013). Across studies with significant findings, three proposed a clear age threshold of five (Winqvist et al., 2001) or six years of age (Kadan-Lottick et al., 2010; Link et al., 2006) under which treatment was associated with increased risk of impairment. One further study suggested that risk gradually decreased with increasing age at diagnosis (Krull, Brinkman, et al., 2013). However, upon further examination, Link et al. (2006) found wider variation in performance in participants receiving CRT at younger ages, and therefore speculated that this result may reflect a small subset of participants with particularly low scores.

Conclusions

The majority of studies suggested that younger age at diagnosis (and subsequent treatment) was associated with poorer cognitive outcomes in later life, for both CNS and non-CNS cancers. There is insufficient evidence to suggest that this effect is specific to CRT as many of the included studies did not differentiate CRT survivors. Nonetheless, two studies suggest an interaction between age at diagnosis and CRT and one further study suggests that they are equal risk factors for cognitive impairment. There is also a suggestion of a critical threshold around age five or six years of age in several studies, although this is opposed by studies that found negative correlations between age at diagnosis and later cognitive functioning.

Time since diagnosis

Ten studies (3 CNS, 7 non-CNS) examined the impact of time since diagnosis/treatment or age at assessment on cognitive outcomes. Of the five studies that investigated time since diagnosis specifically, only one suggested that impairment in executive functioning increased with time since diagnosis (Krull, Brinkman, et al., 2013). Alternatively, of the five studies that investigated age at assessment, two concluded that older age at assessment was particularly associated with poorer visuomotor abilities (Schuitema et al., 2013; Schuitema et al., 2015), two CNS studies failed to find any effect (Ellenberg et al., 2009; Reimers et al., 2003), and one conversely concluded that younger age at assessment was associated with increased risk of impairment, but only on the task efficiency dimension of a self-report measure of neuropsychological functioning (Kadan-Lottick et al., 2010). In sum, findings were mixed depending on whether time since diagnosis or age at assessment was investigated.

CRT dosage

Thirteen studies (3 CNS, 9 non-CNS, 1 both) investigated the effects of increasing CRT dose on cognitive functioning in long-term childhood cancer survivors.

CNS studies

Of three CNS studies, two concluded that higher CRT dosage was related to increased impairment; Armstrong et al. (2010) found location and dose-response effects, with higher dose CRT to the temporal region (but not other regions) predicting increased problems with memory and task efficiency. Reimers et al. (2003) utilised BED (a measure of biologically effective dose), which was significantly negatively correlated to verbal IQ, also showing a dose-response effect. The remaining study did not find any significant effect of CRT dose (Maddrey et al., 2009).

Non-CNS studies

Five studies compared ALL survivors who received either 18Gy or 24Gy, reflective of changing treatment protocols over time. Of these studies, two suggested that both 18Gy and 24Gy subgroups demonstrated significant impairment, with no additional risk of impairment for CRT doses above 24Gy (Kadan-Lottick et al., 2010; Krull et al., 2014). Another two studies found statistically significant impairment in participants who had received 24Gy (but not 18Gy) in immediate recall (Armstrong et al., 2013), and intelligence, memory, and attention (Krull, Brinkman, et al., 2013), although the latter study also found academic impairment after 18Gy and chemotherapy. The remaining study by Harila et al. (2009) did not find any

significant difference in IQ amongst participants treated with 18Gy or 24Gy, and both subgroups achieved scores in the average range.

A further two non-CNS studies with mean CRT dose 22.5Gy also concluded that higher CRT dosage was an additional risk factor for impaired neurocognitive outcomes (particularly visuomotor abilities) and poorer white matter integrity (Schuitema et al., 2015; Schuitema et al., 2013). Only two studies of ALL survivors failed to identify any association between similar CRT doses and later cognitive functioning (Krull, Zhang, et al., 2013; Link et al., 2006).

Finally, Ellenberg et al. (2009) compared CNS survivors treated with mean dose 36.3Gy CRT, non-CNS survivors who received 24Gy CRT, and non-irradiated non-CNS survivors across four self-reported cognitive factors. Findings suggested a dose-response effect on task efficiency and significant effects of CRT on memory, though there was no difference in memory scores between CRT subgroups who received different doses.

Conclusions

Across thirteen studies, nine (69%) found dose-response effects of CRT on neuropsychological functioning, suggesting similar effects across cancer types. It is important to note that mean CRT dosage was generally higher across CNS studies than non-CNS studies, although many studies examining ALL survivors also suggested impairment still exists at lower doses. There was an emerging consensus that participants were more impaired across several domains after 24Gy, with some studies suggesting no effect of 18Gy except on more complex neuropsychological processes such as fluency and flexibility. Some studies further suggested that the

effects of 18Gy were similar to those observed in participants treated with chemotherapy, indicating some non-specific treatment effects. However, no dose effects of chemotherapy were observed in participants who received both CRT and chemotherapy, suggesting that the effects of chemotherapy are nullified by the much larger effects of CRT.

Anatomical Correlates

Seven studies (2 CNS, 5 non-CNS) also used neuroimaging to identify specific effects of CRT on brain structures and activity, and their relationship to cognitive functioning. Of studies that examined brain structures, two found that smaller (right) hippocampal volume was associated with memory impairment in ALL and brain tumours survivors (Armstrong et al., 2013; Jayakar et al., 2015). Memory problems were also associated with CRT to the temporal region in one self-report CNS study (Armstrong et al., 2010) and a further non-CNS study which specified problems with immediate memory (Armstrong et al., 2013).

Furthermore, several studies suggested that participants treated with CRT and chemotherapy showed lower total brain volume (Armstrong et al., 2013; Edelmann et al., 2014; Jayakar et al., 2015), however Jayakar and colleagues (2015) proposed that whole brain volume is affected in all brain tumour survivors and only subcortical structures are uniquely affected by CRT. This conclusion is supported by Reimers et al.'s (2009) findings which showed that tumour site in the cerebral hemisphere (but not subcortical structures of the posterior fossa or the midbrain) was a strong predictor of lower cognitive function in a mixed sample that did not differentiate CRT and chemotherapy. Conversely, Krull et al. (2014) suggested a feedback loop

whereby increased activation in subcortical regions may be due to reduced inhibition from cortical regions, affecting the overall efficiency of neurocognitive processes. Daams et al. (2012) detected some compensatory activity in other brain regions (familiar in normal ageing), but this was not sufficient to improve cognitive functioning.

A further two studies concluded that ALL survivors treated with CRT demonstrated a reduction in white matter volume and thickness (particularly affecting fibre tracts in frontal, temporal, and parietal regions which can have widespread effects on cognition when damaged) and memory impairment, consistent with a pattern of early or accelerated ageing (Edelmann et al., 2014; Schuitema et al., 2013).

Discussion

Although there is a substantial body of literature documenting a range of cognitive deficits in childhood cancer survivors who received CRT, few studies to date have examined the impact of CRT on cognition beyond ten years. This review has examined neurocognitive outcomes of childhood cancers an average of 22 years post-treatment across 21 studies. Differentiating risk factors for adverse neurocognitive outcomes is a complex process, as evidenced by the wide variation across studies in methods of analysing and reporting specific effects of CRT. Nonetheless, it is possible to draw some conclusions regarding the effects of CRT on cognitive functioning in adult survivors of childhood cancers.

Neurocognitive outcomes in CRT survivors

Overall findings across five domains of cognitive functioning suggest that CRT is more likely to have unique enduring effects on memory, attention, and processing speed than intelligence and general executive functions.

Whilst studies were mixed in their conclusions regarding the effects of CRT beyond other treatments on intellectual functioning, the majority found that IQ remained within the average range, consistent with reviews of the paediatric literature (Roman & Sperduto, 1995). This is an important distinction to make as, although it is possible that CRT may result in significant declines in IQ and reduced cognitive reserve over time, there is little evidence that IQ is impaired relative to population norms.

Findings from current studies up to 30 years post-treatment support non-linear models indicating an attenuation in decline in IQ over time, such as the model proposed by Spiegler et al. (2004), and further demonstrate that continued decline is only evident in survivors treated with CRT (Harila et al., 2009). Furthermore, there is also evidence in the present review for idiosyncratic trajectories in cognitive functioning; Krull, Zhang, et al. (2013) found that almost half of their ALL survivor sample treated with CRT did not demonstrate any significant decline in IQ, contrary to the overall finding of significant decline. Individual differences are also found in the paediatric literature, with some studies even reporting improvement in several participants (e.g. Vigliani, Sichez, Poisson, & Delattre, 1996).

The profile of memory problems identified in adult survivors of childhood cancers treated with CRT is largely consistent with early onset of cognitive ageing.

Specifically, studies indicate that delayed and working memory are most affected,

suggesting ineffective encoding or consolidation of new information. The present review also suggested that chemotherapy may affect basic memory skills in adult survivors, and the effects of CRT are specific to more complex memory tasks. This pattern of impairment is also observed in the development of dementia in older adults, with more complex tasks affected by early declines. Some studies have even suggested that this profile has clinical utility for early detection, for example Welsh and colleagues (1991) found that scores on a delayed recall task differentiated early Alzheimer's Disease patients from healthy controls with better than 90% accuracy. However, the difference between dementia sufferers and the current population is in functional impairment; Armstrong et al. (2013) did not find a difference in employment rates between participants treated with different doses of CRT and therefore suggested that deficits in middle adulthood may be more reflective of mild cognitive impairment, which is often considered to be a precursor to dementia (Petersen, 2004).

Findings also suggested that attention may be specifically affected by CRT; attention span and variability were affected in some studies, especially in non-CNS survivors. Processing speed was also affected by CRT, particularly on visuomotor tasks. A key consideration interpreting these results is the interaction of different cognitive abilities. Whilst study of cognition necessitates that it is divided into discrete domains of functioning, it is likely that domains are inter-related i.e. deficits in one domain may have a significant impact on other domains. Early information processing models proposed that the brain has a limited capacity to input, store, and respond to external information and other domains are therefore reliant on attention (Broadbent, 1958). More recent models developed from studies with childhood brain

tumour survivors have also suggested that processing speed, attention, and working memory are interrelated, and have further effects on IQ (King et al., 2017; Palmer, 2008; Wolfe et al., 2012). The results of included studies are largely consistent with these models, as deficits are identified across processing speed, attention, and working memory, and Krull, Zhang, et al. (2013) found that observed decline in IQ was more associated with current attention deficits than traditional risk factors such as CRT dose or age at diagnosis.

Finally, examination of general executive functions such as fluency, flexibility, organising, and inhibition did not highlight significant effects of CRT. A minority of studies suggested some effect on set-shifting, although this may be related to deficits in attention and processing speed. The same studies also found a significant impact of emotional distress on executive functioning, suggesting that CRT is not a primary risk factor in predicting later executive impairment.

Risk factors

The majority of included studies suggested that younger age at diagnosis continues to be associated with poorer neurocognitive outcomes up to 34 years after treatment, consistent with robust findings in the paediatric literature (e.g. Duffner, 2010).

However, it is not clear whether this effect is specific to CRT treatment, as many of the included studies examined mixed treatment samples. It is possible that the effects of age at diagnosis are not specific to CRT treatment as this risk factor has also been shown to predict adverse effects of chemotherapy (Krappmann et al., 2007).

Furthermore, closer inspection of data in the younger subgroup was also found to be more scattered, suggesting that severe damage may only occur in a minority of participants treated at a younger age.

When time since diagnosis was examined, no associations were indicated with later neurocognitive outcomes. However, significant relationships between age at assessment and impairment, particularly in visuomotor functioning, were observed. Crucially, Ellenberg et al. (2009) noted that age at diagnosis and age at assessment have independent effects on cognitive outcomes, and therefore suggested that by using time since diagnosis in studying the effects of ageing, the magnitude of both the ageing-effect and the impact of age at diagnosis are masked. It is therefore possible that studies using time since diagnosis failed to detect ageing effects as a result of not controlling for age at diagnosis, rather than because there was no effect. Further research in this population is required examining age at assessment to clarify the current mixed findings.

Dose-response effects of CRT were also observed across most studies, consistent with findings from reviews examining effects of CRT earlier in the lifespan (Armstrong et al., 2004; Roman & Sperduto, 1995). Moreover, results from non-CNS studies comparing survivors treated with 18Gy and 24Gy indicated that, although most cognitive domains are affected after 24Gy, more complex neuropsychological abilities may be especially sensitive to CRT, as they were affected after lower doses.

CRT and cancer type

Given that both CNS and non-CNS studies found dose-response effects, and average doses were higher in CNS studies, it could be hypothesised that CNS survivors would demonstrate greater impairment. Certainly, deficits in IQ were only found in

CNS studies, however no notable differences were observed between CNS and non-CNS survivors in memory, attention, and processing speed domains as a result of CRT. Minimal differences were also observed in risk of cognitive impairment resulting from age at diagnosis or time since assessment according to cancer type.

Although performance on neuropsychological tests did not differ with cancer type, CNS survivors may have been more functionally impaired; Gurney et al. (2009) found that adult survivors of childhood CNS cancer show greater deficits in educational attainment, employment, and marital status than either sibling controls or non-CNS survivors. Further research into the psychosocial impact of childhood cancer treatment is necessary to clarify the differences in late effects according to cancer type.

Mechanisms of CRT resulting in cognitive decline

Although only a limited array of studies were included in the present review, which used diverse measures to examine neurological structures and mechanisms underlying CRT, several studies suggested that memory impairment was associated with frontal and temporal cortical thickness and smaller hippocampal volume. These findings are consistent with neuroimaging studies of childhood brain tumour survivors which revealed abnormal patterns of hippocampal development after irradiation, particularly in the right hippocampus (Nagel et al., 2004; Riggs et al., 2014).

Furthermore, there was some consensus that poorer neuropsychological performance was associated with reduced white matter integrity and volume. Specifically, poorer

white matter integrity in frontal, parietal, and temporal tracts was highlighted; these tracts are known to myelinate at a later age than other brain regions and may therefore somewhat explain the effects of age at diagnosis on later cognitive functioning (Tau & Peterson, 2009). There were also notable similarities between adult survivors of childhood cancers and Alzheimer's Disease patients in brain structure, white matter (as measured by fractional anisotropy [FA]), and oscillatory activity (Daams et al., 2012; Parente et al., 2008). Memory function in particular, was related to higher FA (Edelmann et al., 2014). Higher FA was also directly related to age at assessment, suggesting that white matter continues to decline as the brains of childhood cancer survivors age.

Currently, there is mixed evidence regarding whether poorer neurocognitive outcomes are a result of CRT specifically, and the majority of studies included in this review found alterations in white matter regardless of treatment type. There have been several proposed mechanisms by which cancer treatment may affect the brain including: glial scarring and axonal injury, vasculopathy leading to ischaemia, decreased myelin, and white matter compaction. There is evidence that both chemotherapy and CRT can: kill oligodendrocytes (myelinating cells) resulting in reduced myelin (Kurita et al., 2001; Smith, 1975); cause vasculopathy leading to ischaemia and white matter necrosis (Morris, Bywaters, & Hopewell, 1996); and limit neural repair by damaging progenitor cells (differentiating cells) which usually maintain white matter integrity and stimulate hippocampal neurogenesis (Fukuda et al., 2005). Furthermore, these patterns of impairment may not be specific to any type of cancer treatment as increased FA has also been observed after brain injury (e.g. Wilde et al., 2008).

Methodological limitations of included studies

It is important to consider limitations in the methodology of the discussed studies.

Although the vast majority of the included studies utilised standardised neuropsychological tasks, two studies measured self-reported neurocognitive functioning. It is questionable whether these measures are representative of ability, though some studies have suggested that self-reported cognitive data correlate with performance-based assessment and neuroimaging (De Groot et al., 2001; Mahone, Martin, Kates, Hay, & Horska, 2009).

Additionally, the majority of studies used retrospective designs, and therefore information regarding premorbid or baseline neurocognitive functioning was not available. Cross-sectional designs may fail to detect an effect of CRT if individuals with high premorbid IQ (and associated greater cognitive reserve) are included as significant decline may not result in impairment at the point of evaluation. Indeed, this disparity was highlighted in the present results, and therefore findings from retrospective studies should be interpreted with a degree of caution. Furthermore, additional studies have highlighted the presence of impairment at baseline due to the malignancy itself, further confounding the effects of CRT (Armstrong et al., 2004).

Other limitations within the included studies are more concerned with feasibility within a very complex area of study. Most patients who undergo CRT also receive other medical interventions that are proposed to also have adverse effects on cognitive functioning including surgery and chemotherapy. Ideally, treatments would be isolated and compared to each other and healthy controls, yet it is infinitely more common that patients receive at least two treatment modalities. Even in studies

comparing participants who received a combination of CRT and chemotherapy to participants who only received chemotherapy, it is difficult to conclude that greater effects in the former group are attributable to CRT. Moreover, individual tolerance to CRT is variable, and may interact with concomitant chemotherapy to lower impairment thresholds beyond the effects of chemotherapy alone (Rottenberg, 1991). Furthermore, assignment to particular treatment protocols is likely to be influenced by factors such as diagnosis, and severity of disease, thus differences in cognitive outcomes could be attributable to pre-existing differences rather than treatment effects (Roman & Sperduto, 1995). Although it is not possible to entirely control for the many interrelated risk factors in measuring neurocognitive outcomes, wider use of multivariate analysis better allows for the study of these interactions; 14 of the 21 included studies used regression analyses in differentiating the effects of CRT and may therefore have drawn more reliable conclusions about its specific effects.

Implications and future directions

Knowledge of likely deficits and risk factors is important for researchers as they strive to reduce neurotoxicity whilst maintaining treatment effectiveness. In light of findings regarding the effects of CRT at younger ages, recommendations have been made to avoid or delay CRT in brain tumour patients under three years old, though the outcomes of these studies are mixed (Bouffet, 2010; Geyer et al., 2005; Heideman, 2001). Other efforts made to reduce the impact of identified risk factors include reducing CRT dosage (Duffner, 2010), and use of conformal radiotherapy which uses 3D imaging to attempt to spare surrounding normal tissues (Conklin, Li, Xiong, Ogg, & Merchant, 2008).

Recently, emphasis is shifting towards neuroimaging research that may improve understanding of mechanisms of CRT damage. Advances in understanding of the underlying biology of cancers may allow future treatments to be tailored accordingly, for example evidence is increasing that medulloblastoma is comprised of a group of molecularly distinct tumours rather than a single disease entity, which may require a unique treatment protocol (Gajjar et al., 2004). Current neuroimaging studies indicating accelerated ageing in the white matter of adult survivors of childhood cancers also highlight the need to provide continued follow-up for this population. Adult survivors may also benefit from early screening and/or diagnosis of mild cognitive impairment as early detection may facilitate access to cognitive interventions such as the 12-week computerised intervention targeted at working memory developed by Hardy and colleagues (2011).

Although findings of the present review suggest late effects on multiple cognitive domains and neuroanatomic substrates, the predictability of these deficits continues to be reduced by multiple confounding factors, including individual factors.

Armstrong et al. (2004) propose that individual vulnerability to CRT is complex, leading to severe damage in only a minority of patients. Longitudinal studies are needed to fully characterise enduring deficits and determine factors that place individual patients most at risk. Future research should also use multidisciplinary measures to provide convergent evidence of deficits and contributing mechanisms.

Limitations

There are several limitations of the present review that must be considered. Firstly, fewer CNS studies met inclusion criteria than non-CNS studies, therefore the

conclusions drawn from these may be less reliable. Secondly, only three risk factors are considered in detail, which may not fully explain the variation in findings; other risk factors such as tumour location and gender may also have shown significant effects. Additionally, although studies which compared to chemotherapy-only subgroups in their design were included, findings were not compared to separate studies of survivors who received chemotherapy alone. Moreover, the present review did not distinguish between different chemotherapeutic agents despite evidence to suggest that different ALL chemotherapy treatment regimens (without CRT) result in different rates of acute neurotoxicity and leukoencephalopathy according to factors such as exposure with repeated intravenous methotrexate (MTX), and choice and timing of triple intrathecal therapy (Mahoney et al., 1998). Finally, given that many of the included studies examine survivors treated under historic ALL protocols, the findings are not generalisable to the current ALL population. However, findings continue to be relevant to brain tumour survivors treated on contemporary protocols.

Conclusions

Despite ongoing difficulties differentiating the effects of CRT from other treatments and associated risk factors, there is growing evidence to suggest that CRT continues to specifically adversely affect memory, processing speed, and attention in adult survivors of childhood cancers beyond the effects of chemotherapy alone.

Furthermore, younger age at diagnosis and CRT dosage continue to be significant risk factors for adverse cognitive outcomes in older survivors, regardless of cancer type. However, many additional factors need to be considered in the interpretation of these findings, including the significant interactions between different cognitive

domains, individual differences, and multiple risk factors that may predict cognitive decline years after treatment.

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Part 2: Empirical Paper

Neurocognitive and psychosocial late effects of cranial radiotherapy in young adult survivors of adolescent cancers

Abstract

Aims: The aim of this study was to provide a preliminary overview of how receiving cranial radiotherapy (CRT) during adolescence affects neurocognitive, social, and psychological functioning in adulthood. Three additional risk factors (radiotherapy dosage, time since treatment completion, and additional treatments) were also evaluated.

Method: Twenty-five adult survivors of brain tumours treated with CRT were compared with a control group of 17 survivors of non-CNS malignancies treated with radiotherapy elsewhere in the body. Participants completed a brief IQ assessment, an intrusive imagery interview, and self-report questionnaire measures of social functioning, depression, and anxiety.

Results: Few differences were identified between survivors treated with CRT and controls across domains of social and psychological functioning, though participants treated with CRT reported significantly greater problems with memory, and were five times more likely than controls to be single. Results indicated generally positive social adjustment, and IQ scores and levels of depression and anxiety were comparable to the normal population. Total radiotherapy dosage and receiving chemotherapy in addition to radiotherapy were significant predictors of IQ, regardless of where RT was administered in the body. Time since treatment and surgery did not predict late effects across any domain.

Conclusions: Although results may be suggestive of a protective effect of age such that survivors treated with CRT during adolescence may not necessarily suffer the same adverse effects as those irradiated during childhood, this conclusion must be interpreted with great caution, in view of substantial methodological limitations. Implications and the need for further research are discussed.

Introduction

Onset of cancer in adolescence is a relatively rare occurrence, accounting for less than 2% of cancers in the US and less than 1% in Europe (Birch, Alston, Quinn, & Kelsey, 2003; Bleyer, Viny, & Barr, 2006; Cancer Research UK, 2018). Although distinct in tumour epidemiology, incidence, and survival rates, there is a common trend for the adolescent and young adult age group to be incorporated with either childhood or older adult populations, thus the experience of cancer in adolescence remains poorly understood.

Alongside rising incidence rates in adolescent cancers (Cancer Research UK, 2018), advances in medical technology, including radiotherapy (RT), have resulted in improved survival rates since the 1970s (Siegel, Miller, & Jemal, 2018).

Consequently, the long-term or late effects of these treatments are becoming an increasingly relevant concern for a growing population of adult survivors of adolescent cancers. Despite the well-established literature on the adverse outcomes of cranial radiotherapy (CRT) for survivors of childhood cancers, few studies to date have distinguished the unique psychosocial and neurocognitive outcomes of cancer when diagnosed in the teenage years.

Developmental characteristics of adolescents

Adolescence is typically experienced as a turbulent stage of development, characterised by a multitude of physical, neurological, emotional, social, and cognitive changes. Although cancer patients of all ages are said to experience a universal set of disruptions (Rowland, 1990), individuals diagnosed with cancer

during adolescence are likely to face additional challenges due to the important developmental ‘tasks’ associated with this period.

Psychosocially, adolescence is concerned with increasing autonomy and shifts in attachment from parents to peers, thus socialising with peers becomes increasingly important (Ryan, 2001). Adolescents are also expected to develop a personal value system and sense of self (Erikson, 1956), alongside an increased ability for abstract reasoning and logical thought (Piaget, 1952). Hormonal changes occurring during this period lead to alterations in physical appearance and body image, and emerging intimate relationships, which are often accompanied by increased anxiety and self-consciousness (Buchanan, Eccles, & Becker, 1992). In addition to the significant psychosocial and hormonal challenges faced during this period, the adolescent brain also undergoes significant reorganisation, beginning in puberty and continuing into early adulthood (Konrad, Firk, & Uhlhaas, 2013). This reorganisation primarily involves maturation of white matter networks which support the development of advanced cognitive abilities (Giedd et al., 1999; Giedd et al., 1996; Konrad et al., 2013; Mulhern et al., 2001). Whilst the high cortical plasticity of the adolescent brain is crucial for the intellectual and emotional development associated with this life stage, it may also increase vulnerability to harm from treatments such as CRT.

Current knowledge of the late effects of CRT

Late effects, as distinguished from acute effects, are those that emerge months or years after completion of treatment, and are assumed to be chronic and progressive in nature. It is widely accepted within the paediatric literature that children receiving cranial or craniospinal radiotherapy are at higher risk for impaired functioning later

in life, though the applications of this research to survivors of adolescent cancers is yet unclear.

Neurocognitive functioning

Since the 1980s, many reviews have evaluated the impact of CRT on cognitive functioning in survivors of childhood brain tumours and acute lymphoblastic leukaemia (ALL). Although late effects have been reported across many domains of neuropsychological functioning, IQ scores have historically provided a benchmark for change after cancer treatment (Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004). Early reviews reported declines in IQ of up to ten points after CRT treatment (e.g. Cousens, Waters, Said, & Stevens, 1988), whilst subsequent reviews revealed only mild intellectual declines over time, with most survivors achieving IQ scores within the average range (Mulhern et al., 2004; Roman & Sperduto, 1995).

Closer examination of survivors has allowed the identification of vulnerable subgroups. Specifically, more substantial deficits have been recognised in groups of children treated with CRT at a younger age, and with higher doses (Grill et al., 1999; Kieffer-Renaux et al., 2000; Silber et al., 1992). Dose-response relationships are particularly well-documented between CRT dosage and later intellectual functioning, for example, Silber et al. (1992) found that medulloblastoma patients treated with 36 Gray (Gy) CRT scored 8.2 IQ points below those treated with 24Gy, who scored 12.3 points below those who received 18Gy. Although there is some evidence that survivors treated with low dose CRT show observable neurocognitive deficits (e.g. Robinson, Fraley, Pearson, Kuttlesch, & Compas, 2013), IQ decline is most frequently reported in studies of patients who received doses greater than 24Gy (e.g. Mulhern, Fairclough, & Ochs, 1991). Further research has extended these findings to

reveal an interaction between CRT dosage and age; in a prospective and randomised clinical trial conducted by the Pediatric Oncology Group in the US, survivors who were younger at the time of CRT (<8.8 years of age) and treated with a higher dose showed a 10-15 point decline in IQ, whereas older children did not demonstrate the same deficit (Mulhern et al., 1998). There is ongoing controversy, however, about the effect of age on IQ according to the chosen definition of 'younger age'. Many studies have arbitrarily determined cut-offs of between two and 12 years of age to compare outcomes across (e.g. Armstrong, Gyato, Awadalla, Lustig, & Tochner, 2004; Bledsoe, 2016; Moore, Ater, & Copeland, 1992; Mulhern et al., 1998; Palmer et al., 2001; Pulsifer et al., 2015), thus it remains largely unclear how survivors treated during adolescence are affected.

Decline in IQ is broadly recognised to be secondary to white matter changes in the brain, which increase with both higher CRT dosage and younger age at time of treatment (Corn et al., 1994; Mulhern et al., 2001; Mulhern et al., 1999; Reddick et al., 2000). All cancer treatment protocols prescribed to children and adolescents are constrained by the balance between successful disease control and adverse effects on cognition. For CRT, it is proposed that the therapeutic action of ionising radiation used to kill malignant cells also affects adjacent healthy cells in the central nervous system (CNS), leading to cognitive dysfunction. Proliferating cells such as glial and vascular endothelial cells have been identified as especially sensitive to irradiation and may be responsible for the white matter changes associated with declining IQ (Kudo et al., 2014). However, the hippocampal granule cell layer in the dentate gyrus (the major site of adult neurogenesis) has been evidenced in animal models to be damaged by CRT at much lower doses than those needed to affect glial or neural

brain cells (Monje & Palmer, 2003), therefore it is reasonable to assume that hippocampal functions may be impaired at lower doses than those needed to affect IQ.

The hippocampus has been shown to have several important roles in memory, learning, and spatial processing (Bartsch, 2012), and is also implicated in the development of post-traumatic stress disorder (PTSD) as part of the neural basis for involuntary memory retrieval (Brewin, Gregory, Lipton, & Burgess, 2010; Moscovitch, 1995). Although previous research has suggested CRT-induced impairment in most of the diverse range of hippocampal functions, including memory and spatial navigation (Armstrong et al., 2000; Pereira Dias et al., 2014), few studies have focused on the impact of CRT on involuntary memory retrieval, and none to date have examined an adolescent population. Furthermore, given that both white matter networks and several hippocampal brain regions show unique developmental trajectories during adolescence, it is possible that the impact of CRT on hippocampal functions in this age group may differ from both younger children and older adults.

Psychosocial functioning

The focus of late effects research is also starting to broaden to psychological and social outcomes, as it has been proposed that cognitive and psychosocial functioning may be bi-directionally related. For example, Maddrey et al. (2005) suggested that the majority of brain tumour survivors in their study were unable to drive as a result of CRT-related visuospatial, motor, and executive impairments, which served to further restrict vocational and social opportunities. Moreover, several large cohort studies have identified CRT specifically as a risk factor for poorer health-related

quality of life, mediated by neurocognitive outcomes, in adult survivors of childhood brain tumours (Hudson et al., 2003; Zeltzer et al., 2008; Zeltzer et al., 2009).

Crucially, from the few studies that have investigated the relationship between age at treatment and subsequent psychosocial functioning, it seems that different stages of development may be associated with specific deficits. Aarsen et al. (2006) found that survivors who received treatment in adolescence reported lower social adjustment, based on a health-related quality of life measure, compared with children treated at younger ages. Receiving treatment for cancer as an adolescent typically results in renewed dependence on parents, and a reduced ability to participate in peer activities, which may threaten the accomplishment of the key developmental tasks of adolescence. Failure to achieve these tasks could predispose adolescent cancer patients to problems with psychosocial functioning that extend into adulthood (Stam, Grootenhuis, & Last, 2005).

Similarly, having cancer in adolescence presents many emotional and psychological challenges, both during treatment and in the survivorship stage. Physical changes caused by cancer treatments (including hair loss and scarring) may substantially affect developing body image and sense of identity, and the requirement some adolescents face to prematurely confront their own mortality is likely to lead to difficulty in integrating their experiences into normal life once treatment has ended. Indeed, many adult survivors of adolescent cancers report increased post-traumatic stress (Hobbie et al., 2000) and psychological distress (Kazak et al., 2010) compared to survivors of childhood cancers.

Moreover, the evidence regarding the emotional late effects of CRT is mixed, and based on only a small corpus of studies. Whilst some studies have found no relationship between CRT and depression (Roman & Sperduto, 1995), others have suggested that depression increases with years after treatment and is possibly related to fatigue, cognitive impairment, and the need for greater family support (Armstrong, Goldstein, Cohen, Jo, & Tallent, 2002).

Additional risk factors

Besides the previously discussed risk factors of higher CRT dosage, and younger age at treatment, a multitude of other factors are proposed to affect neurocognitive and psychosocial outcomes in adult survivors of childhood and adolescent cancers.

Ullrich and Embry (2012) discuss four broad categories of risk factors for neurocognitive dysfunction: cancer-related factors (such as cancer type and tumour location); survivor-related factors (such as gender, baseline level of functioning, and time since treatment); treatment factors (such as surgery, chemotherapy, and CRT dosage); and environmental factors (such as school absences and family support).

While the benefits of rigorous study design are universally acknowledged, it is not feasible for research in this area to account for all potentially confounding factors, even in large trials (Armstrong et al., 2004). The majority of studies evaluating the specific effects of CRT in cancer survivors must prioritise key variables according to the aims of the study and methodological limitations. Although the present study is primarily concerned with the effects of CRT in adolescence, it will also consider the impact of three additional risk factors proposed to have significant effects on neurocognitive and psychosocial outcomes. Besides age, the two most widely-

documented risk factors in both the brain tumour and leukaemia literatures are those of CRT dosage and concurrent treatments, especially chemotherapy (Duffner, 2004; Duffner, 2010; Roman & Sperduto, 1995). Time since completing treatment is also highlighted as an important risk factor, particularly for intellectual functioning, as longitudinal studies of brain tumour patients have revealed increasing declines in IQ over time (Mulhern et al., 2001; Palmer et al., 2003; Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001). Furthermore, recent work has focused on defining the relationships between risk factors as it is recognised that they may not act on outcomes independently; for example, several studies propose a multiplicative effect of CRT and chemotherapy on brain integrity, even when the CRT dose is relatively low (Brown et al., 1992; Correa et al., 2004; Deangelis, Yahalom, Thaler, & Kher, 1992; Gavrilovic, Hormigo, Yahalom, Deangelis, & Abrey, 2006).

Rationale and aims of the study

Treatment of adolescents with cancer is challenging, particularly in a healthcare system that has historically been dichotomised into paediatric and adult care. Only recently have health policy initiatives started to recognise adolescent cancer patients as a distinct population with unique needs. In light of guidelines published by the National Institute of Health and Clinical Excellence (NICE, 2005), adolescents are now mostly treated in dedicated teenage and young adult cancer units with specialised multidisciplinary teams and late effects services. However, compared with the sizeable body of literature that exists for survivors of childhood cancers, there is limited research into late effects of cancer diagnosed in adolescence to inform these services. Improved understanding of neurocognitive and psychosocial

outcomes is critical in supporting healthcare providers to tailor services for cancer survivors according to their specific needs.

Given the paucity of studies investigating the late effects of adolescent cancers, the aims of the present study are largely exploratory. In accordance with the neurocognitive late effects literature, the present study will investigate the effects of CRT on IQ and intrusive imagery (hypothesised to be related to hippocampal functioning) in adult survivors of adolescent cancers treated with minimum CRT doses of 24Gy. It is hoped that these findings will be enriched by the additional consideration of psychosocial late effects, as few studies to date have examined the impact of CRT during adolescence across more than one domain of functioning.

Furthermore, although many studies investigating treatment effects have compared cancer survivors to healthy controls, this design overlooks the likely psychosocial impact of diagnosis and treatment. Consequently, the current study compares adult survivors of cancers of the central nervous system (CNS) treated with CRT to a control group of solid tumour survivors who experienced many of the same treatments (such as chemotherapy and surgery) and acute sequelae of cancer treatment (such as absence from school and restricted peer interaction), except they received non-CNS radiotherapy to parts of the body other than the cranium. It is hoped that results from this study will provide a preliminary overview of how receiving radiotherapy to the brain during adolescence, amongst several other risk factors, affects multiple domains of functioning in later life, establishing a precedent upon which future research can be built.

Research questions

Primary question:

1. Do the late effects of receiving radiotherapy to the brain (CRT) in adolescence differ from those associated with receiving radiotherapy elsewhere in the body across domains of neurocognitive, social, and psychological functioning?

Secondary questions:

2. How are the same domains of functioning affected by the risk factors of i) time since treatment, ii) radiotherapy dosage, and iii) the use of additional treatments including chemotherapy and/or surgery)?
3. How do risk factors interact to affect later functioning?

Method

Participants

All participants were recruited from a specialist teenage and young adult cancer service at a London NHS hospital. Potential participants were identified from a database of patients who were diagnosed and treated for cancer between 1999 and 2016. To be eligible for inclusion, participants must: 1) have received radiotherapy within a minimum dosage of 24Gy as part of their cancer treatment, 2) have received treatment during adolescence (between 12 and 18 years of age), 3) be aged 18 to 30 at the time of evaluation, and 4) have completed treatment a minimum of two years prior to participation in the study. Exclusion criteria included a history of traumatic brain injury, and genetic diagnosis with known association with neurocognitive impairment (such as Down's Syndrome).

Of a total of 103 potential participants who met inclusion criteria, 43 (42%) accepted to participate. Power calculations revealed that the sample size was adequate to detect a medium-to-large effect size assuming two-tailed alpha set to .05.

Twenty-five participants received radiotherapy to the brain and CNS (CRT), and 18 received non-CNS radiotherapy (RT) elsewhere in the body, depending on the type of cancer they were treated for (see Table 1). One participant was excluded from analysis due to previous brain injury not disclosed until participation. Within survivors treated with CRT, 14 received localised or focal RT specific to the tumour site, seven received craniospinal RT with a boost to the primary tumour site, and two received craniospinal RT only. Type of RT was not recorded for one participant. All controls received non-CNS RT, localised to the site of malignancy.

Table 1.

Types of Cancer within the Sample

	Frequency	Percentage
Brain cancers	n = 25	
Medulloblastoma	8	32
Astrocytoma	4	16
Germinoma	4	16
Ependymoma	2	8
Other	7	28
Controls	n = 18	
Hodgkin's lymphoma	8	44
Ewing's sarcoma	3	17
Testicular	2	11
Breast	1	6
Liposarcoma	1	6
Osteosarcoma	1	6
Other	2	11

Demographics and additional treatment information are presented in Table 2.

Alongside RT, 32 participants also received chemotherapy (16 CRT survivors, 16 controls), and 24 had surgery (16 CRT survivors, 8 controls) as part of their treatment protocol.

Procedure

All eligible participants were sent a letter inviting them to participate in the study, together with an information sheet (see Appendix A, B, and C for study documentation). Participants were invited to express interest in the study either through the return of a tear-off slip or via email. The letter was followed by a phone call approximately two weeks later. All participants were offered a £10 online shopping voucher as compensation for their time. Data were collected in a one-off session lasting approximately 90 minutes, arranged to coincide with participants' other hospital appointments where possible.

Ethics

Ethical approval was obtained from the North of Scotland Research Ethics Service (Ref: 17/NS/0082, Appendix D) and the Health Research Authority (Appendix E). If participants presented with psychological distress during participation in the study, a referral to the psychology service at the hospital was discussed with them. A total of three participants (two from the CRT group, one from the control group) were referred to the psychology service for support with concerns unrelated to participation in the study.

Measures

Demographic and treatment information

Data regarding participants' gender, ethnicity, age at diagnosis and evaluation, cancer diagnosis, treatment received (including additional chemotherapy and/or surgery), RT dosage, relapse, and time since treatment were extracted from the hospital patient information database.

Cognitive Functioning

The Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II; Wechsler, 2011). The WASI-II was used to obtain an estimate of intellectual functioning, measured by intelligence quotient (IQ). The WASI-II is widely used in research, including in studies of cancer survivors, as it allows estimates of IQ scores to be obtained quickly and accurately when a full battery is not feasible. It is comprised of four subtests; two assess verbal abilities (Vocabulary, Similarities) and two assess performance abilities (Block Design, Matrix Reasoning). The battery was standardised using a large and representative US normative sample, aged from 6 to 90 years old. Scores from each subtest are compared to age-specific population norms in order to generate *t*-scores, which are then summed and converted to three standardised scores of verbal comprehension, perceptual reasoning, and full-scale IQ.

For the purposes of the present study, only full-scale IQ (based on all four subtests) was examined. This index score has been shown to be internally consistent in both child and adult populations, with average reliability coefficients of Cronbach's $\alpha = .93$ and $.94$, respectively (McCrimmon & Smith, 2013). Concurrent validity was established with the full Wechsler intelligence scales and measures of academic

achievement, with correlations ranging from $r = .71$ to $.92$ (McCrimmon & Smith, 2013).

Psychological Functioning

The Patient Health Questionnaire-9 items (PHQ-9; Kroenke, Spitzer, & Williams, 2001). The PHQ-9 was used to assess depressive symptomatology. The nine items each represent one of the DSM-IV symptoms criteria for major depression (e.g. ‘poor appetite or overeating’) and are scored on a frequency scale from 0 (‘not at all’) to 3 (‘nearly every day’) over two weeks. The PHQ-9 demonstrated good reliability (Cronbach’s $\alpha = .89$) and good construct validity when compared to other depression measures in the original primary care population for which it was developed (Kroenke et al., 2001) and, more recently, in an adult cancer population (Johns et al., 2013). PHQ-9 scores of 10 or more had sensitivity of 88% and specificity of 88% for major depression, with scores of 5, 10, 15, and 20 representing mild, moderate, moderately severe, and severe depression, respectively (Kroenke et al., 2001).

The Generalised Anxiety Disorder Scale-7 items (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006). The GAD-7 was used to assess anxiety symptomatology. The items are scored in the same way as the PHQ-9, on a frequency scale from 0 to 3. Internal consistency has been shown to be excellent (Cronbach’s $\alpha = .92$), and convergent validity was good, evidenced by strong correlations with other established anxiety measures (Spitzer et al., 2006). Scores of 10 or more showed sensitivity and specificity of 89% and 82%, respectively, and were therefore used as cut-offs in the present study (Spitzer et al., 2006). Scores of 5, 10, and 15 can be

interpreted as representing mild, moderate, and severe levels of anxiety, similar to depression severity on the PHQ-9.

Intrusive Imagery Interview (Glazer, Mason, King, & Brewin, 2012). An Intrusive Imagery Interview was used to assess participants' experiences of intrusive imagery, as intrusive images are prominent in many psychological disorders, including under the 're-experiencing' cluster of PTSD symptoms (American Psychiatric Association, 2013; Brewin et al., 2010). The version of the structured interview used in the present study was developed by Glazer et al. (2012) and used within a healthy population, though it was based on an interview developed by Patel et al. (2007) for use with depressed patients. Following a brief description of intrusive imagery, participants were asked how many intrusive images and/or memories they had experienced over the past week, and then up to two were explored in further detail. Participants were asked to rate the image on several factors on a scale from 0 ('not at all') to 100 ('very much'), including the vividness, the extent to which various emotions accompanied the image (sadness, anxiety, happiness, anger, helplessness, shame, guilt), and the extent to which various senses were engaged (olfactory, taste, auditory, tactile, visual). Participants were also asked to rate the sense of 'nowness' associated with the image, which was defined as "the extent to which it felt like the image was actually happening in the present" (see Appendix F). Five scores were generated from participant responses; the total number of intrusive images experienced over the past week, the emotional intensity, 'nowness', vividness, and sensory associations of these images. Emotions and sensory scores were generated using the highest rating given across the seven emotions and five senses items. Where two images were reported, the highest score

on each variable was used. Where participants reported at least one image, the nature of the images was also classified according to whether they were cancer-related (non-related vs at least one cancer-related).

Social Functioning

The Impact of Cancer for Childhood Cancer Survivors Scale (IOC-CS; Zebrack, 2009). The IOC-CS was developed as a measure of the physical, psychological, and social impact of long-term survivorship, and was used in the present study as a measure of social functioning (see Appendix G). The IOC-CS aims to measure distinct constructs relevant to the young adult cancer survivor population that other existing standardised measures may not evaluate. Initially developed as an 82-item questionnaire from interviews with 64 young adult cancer survivors (Zebrack, 2009), the IOC-CS was later validated in a sample of 519 survivors (Zebrack et al., 2010). Items were refined through factor analysis, revealing eight subscales consisting of 45 items; five subscales (Body and Health, Talking with Parents, Personal Growth, Health Literacy, Socialising) demonstrate a positive impact (e.g. “I like the way my body looks”) and three subscales (Life Challenges, Memory and Thinking Problems, Financial Problems) reflect negative impacts (e.g. “I have a hard time remembering things from long ago”). Items are scored on a five-point scale from 1 (‘not at all’) to 5 (‘very much’), and mean scores are calculated for each subscale. For these eight subscales, Cronbach’s α ranged from .70 to .86, indicating adequate reliability (Zebrack et al., 2010). Items relating to health insurance, which are not relevant to a UK population, were excluded. IOC-CS subscales were also correlated with other established measures of distress, life

satisfaction, and health-related quality of life, indicating good concurrent validity (Zebrack et al., 2010).

The IOC-CS also assesses the impact of cancer on siblings and intimate relationships, although these items were scaled separately as they were not applicable to all respondents. In the present study, only the Sibling subscale was included as the majority of participants completed these items (only three participants did not have siblings), whereas Relationship Concerns (partnered) and Relationship Concerns (non-partnered) were mutually exclusive subscales completed by fewer participants each. Furthermore, Cronbach's α was found to be variable for the relationship subscales, but adequate for the sibling subscale (Zebrack et al., 2010). Instead, a simple measure of relationship status was determined from responses; participants were classified into two groups (single, in a relationship) according to whether they completed the Relationship Concerns (non-partnered) subscale or the Relationship Concerns (partnered) subscale.

Data preparation

Each domain of functioning was examined to ensure that variables met assumptions of normality using the Kolmogorov-Smirnov test and z-scores calculated for skewness and kurtosis. Data were also inspected using box plots and z scores, with cases exceeding ± 3 identified as outliers. IQ scores met all assumptions and no outliers were identified. Scores on the PHQ-9 and GAD-7 demonstrated mild skew which was resolved by square root transformation of both variables. Examination of intrusive imagery variables revealed that whilst nowness was normally distributed, number of images reported was positively skewed, and vividness, and emotion and

sensory scores were negatively skewed. Given that variables would be compared, transformations were attempted on all variables but were not successful, therefore non-parametric tests were used to examine intrusive imagery variables. Furthermore, two outliers identified in number of images reported and one outlier identified amongst sensory scores were identified and excluded from analysis. Of the nine variables comprising the IOC-CS, four were normally distributed (life challenges, body and health, personal growth, health literacy) three showed non-normal distributions due to floor effects (memory and thinking, financial problems, sibling) and two showed ceiling effects (talking with parents, socialising). Transformations were attempted but were not successful on all variables therefore non-parametric tests were also employed when exploring IOC-CS variables.

Participant and treatment-related variables were also examined for normality and outliers. Time since diagnosis was found to be normally distributed. The distribution of RT doses across the sample was significantly skewed, and therefore underwent square root transformation.

Statistical analysis

Data analysis was performed using SPSS, version 24.

Primary question

In addressing the primary research question, initial descriptive analyses were completed to compare IQ scores to population norms, and evaluate depression and anxiety scores according to pre-defined cut-offs to calculate the percentage of participants who were impaired in terms of cognitive or psychological functioning.

CRT and control groups were then compared on all domains and variables using independent samples *t*-tests for continuous data (FSIQ), chi square for categorical data (relationship status, type of intrusive image), and MANOVAs where variables were considered to measure the same construct (psychological functioning [PHQ-9, GAD-7]). Likelihood ratios and exact statistics were used to interpret chi square analyses to preserve power in a small sample. Given that several intrusive imagery and IOC-CS variables were not normally distributed when examined, non-parametric Mann-Whitney tests were used to compare each of the variables in lieu of MANOVA, and alpha was set at .025 to reduce the possibility of type I error in the context of multiple comparisons.

Secondary questions

Three risk factors (time since treatment, RT dosage, and the use of additional treatments including chemotherapy and surgery) were assessed in addressing the second research question. Correlations were completed to examine the relationships between RT dosage and time since treatment with all domains of functioning. Pearson's correlations were used, except for variables which were previously found to violate assumptions of normality, which were investigated using Spearman's correlations. Additionally, alpha was set at .025 to correct for multiple comparisons. Chemotherapy (vs no-chemotherapy) and surgery (vs no-surgery) groups were compared using the same approach employed to assess the primary research question.

To test the third research question, any significant relationships highlighted in planned evaluations of effects of the three risk factors (time since treatment, RT

dosage, additional treatment) across domains of cognitive, psychological, and social functioning were further explored using hierarchical regression analyses to test the effects of risk factors whilst controlling for RT treatment group (CRT vs controls). Any identified significant predictors were then entered into additional regression analyses to assess any interactions between them. All regression models were evaluated with respect to multicollinearity, homoscedasticity, normality, and linearity.

Results

Results are presented in three parts, in order of the research questions. First, the neurocognitive, psychological, and social late effects observed in adult survivors of adolescent cancers treated with CRT are described and compared to those of controls (survivors of cancers treated with RT elsewhere in the body). Secondly, the effects of three risk factors (time since treatment, RT dosage, additional treatments) are presented. Thirdly, the interactions between risk factors evaluated in the second section are explored further.

1. Late Effects of CRT across Domains

Descriptive analyses

Table 2 shows demographic and previous treatment information for all participants, and compares those who received CRT and controls (who received RT not to the cranium). There were no significant differences between the CRT group and controls except for total radiotherapy dose and the number of participants who received concurrent chemotherapy; participants treated with CRT received higher

doses of RT than participants who had RT elsewhere in the body and a greater proportion of the control group received chemotherapy than the CRT group.

Mean scores and *p*-values of test scores between participants who received CRT and participants who received RT elsewhere in the body can be seen in Table 3.

Cognitive functioning

IQ. Across CRT and control groups, all participants scored at least within the average range compared to population norms. Although participants treated with CRT achieved lower IQ scores than controls, this difference was not significant, $t(40) = 0.68, p = 0.500, r = .11$.

Psychological functioning

Depression and Anxiety. Participants were divided around the recommended cut-off point of 10 for moderate depression and anxiety on the PHQ-9 and GAD-7 as summarised in Table 3. Six (24%) participants in the CRT group and three (18%) controls scored in the moderate range or above for depression. Five (20%) participants in the CRT group and three (18%) controls scored in the moderate range or above for anxiety. Using MANOVA and Pillai's trace, there was no significant effect of CRT compared to controls on psychological functioning, $V = 0.073, F(2, 39) = 1.54, p = 0.23$.

Intrusive Imagery. Groups also did not differ significantly on intrusive imagery variables (total number of images reported, vividness,nowness, and emotional and sensory nature of images reported). The type of intrusive images reported showed a trend towards being different across groups; participants treated

Table 2.

Demographic and Treatment Information and Comparison of Groups

	All participants (n = 42)	RT Treatment Group			Concurrent Treatment					
		CRT (n = 25)	Controls (n = 17)	p-value	Chemotherapy (n = 32)	No Chemotherapy (n = 10)	p-value	Surgery (n = 24)	No Surgery (n = 18)	p-value
Mean age at diagnosis, years (SD)	14.8 (2.5)	14.2 (2.5)	15.6 (2.5)	0.689	15.1 (2.5)	13.9 (2.4)	0.196	15.3 (2.6)	14.2 (2.4)	0.156
Range	11-18	11-18	12-18		11-18	11-18		11-18	11-17	
Mean age at evaluation, years (SD)	22.9 (2.3)	22.3 (2.1)	23.6 (2.4)	0.668	23.1 (2.4)	22.1 (2.1)	0.24	22.9 (2.4)	22.8 (2.2)	0.850
Range	18-29	18-26	20-29		20-29	18-25		18-29	20-27	
Mean time off treatment, years (SD)	6.8 (2.6)	6.9 (2.3)	6.7 (3.1)	0.337	6.8 (2.7)	7.1 (2.5)	0.719	6.5 (2.5)	7.3 (2.8)	0.293
Range	2-14	2-11	2-14		2-14	2-9		2-11	4-14	
Gender (%)										
Male	30 (71)	16 (64)	14 (82)	0.300	24 (75)	6 (60)	0.433	17 (71)	13 (72)	0.999
Female	12 (29)	9 (36)	3 (18)		8 (25)	4 (40)		7 (29)	5 (28)	
Ethnicity (%)										
White	32 (76)	19 (76)	13 (76)	0.999	24 (75)	8 (80)	0.742	19 (79)	13 (72)	0.720
Minority	10 (24)	6 (24)	4 (24)		8 (25)	2 (20)		5 (21)	5 (28)	
Mean dose of radiotherapy, Gy (SD)	47.6 (10.4)	51.7 (7.9)	42.2 (11.1)	0.005	46.2 (11.3)	52.8 (3.3)	0.059	52.7 (4.3)	40.1 (12.3)	0.003
Range	24-62	24-62	30-59		24-62	50-59		41-62	24-60	
Chemotherapy (%)										
Yes	32 (76)	16 (64)	16 (94)	0.031						
No	10 (24)	9 (36)	1 (6)							
Surgery (%)										
Yes	24 (60)	16 (64)	8 (47)	0.348						
No	18 (40)	9 (36)	9 (53)							
Previous relapse										
Yes	6 (14)	3 (12)	3 (18)	0.672						
No	36 (86)	22 (88)	14 (82)							

Note: Significant *p*-values are highlighted in bold text

Table 3.

Mean Scores, p-values, and Effect Sizes for Differences between RT Treatment Groups

	N*	All participants Mean (SD)	% impaired (N)	N*	CRT Mean (SD)	% impaired (N)	N*	Controls Mean (SD)	% impaired (N)	p-value	Effect size	
											<i>r</i>	ηp^2
Intellectual functioning												
IQ	42	103.7 (11.7)	0 ^a	25	102.7 (13.2)	0 ^a	17	105.2 (9.0)	0 ^a	0.500	0.107	
Psychological functioning										0.227		0.073
Depression	42	6.6 (4.7)	21.4 ^b (9)	25	7.36 (5.2)	24.0 ^b (6)	17	5.47 (3.6)	17.6 ^b (3)	0.233		0.004
Anxiety	42	5.5 (4.1)	19.0 ^b (8)	25	5.24 (4.3)	20.0 ^b (5)	17	5.82 (3.9)	17.6 ^b (3)	0.675		0.035
Intrusive Imagery												
Total number of images	40	18.7 (40.9)		23	11.8 (12.3)		17	9.5 (12.6)		0.394	-0.137	
Emotions (max. 100)	35	72.4 (24.7)		21	77.1 (20.8)		14	65.4 (29.1)		0.190	-0.224	
Vividness (max. 100)	35	71.8 (23.1)		21	70.1 (30.8)		14	74.3 (24.5)		0.966	-0.001	
Nowness (max. 100)	35	47.4 (34.6)		21	47.6 (37.4)		14	47.1 (31.3)		0.940	-0.014	
Sensory (max. 100)	34	87.4 (24.7)		20	87.1 (22.3)		17	87.7 (14.9)		0.915	-0.020	
Type of images reported	42	<u>N</u>		25	<u>N</u>		17	<u>N</u>		0.069		
No images reported		5			2			3				
Non-cancer related		28			15			13				
At least one cancer-related		9			8			1				

Social functioning								
Life challenges (-)	42	2.20 (0.74)	25	2.26 (0.73)	17	2.09 (0.77)	0.427	-0.125
Body and health (+)	42	3.22 (0.77)	25	3.16 (0.82)	17	3.32 (0.75)	0.521	-0.101
Talking with parents (+)	42	3.85 (1.14)	25	3.86 (1.18)	17	3.82 (1.10)	0.882	-0.024
Personal growth (+)	42	3.43 (0.95)	25	3.44 (1.00)	17	3.42 (0.89)	0.746	-0.052
Memory and thinking (-)	42	2.78 (0.92)	25	3.05 (0.92)	17	2.38 (0.77)	0.009	-0.399
Health literacy (+)	40	3.88 (0.69)	23	3.80 (0.73)	17	3.99 (0.65)	0.492	-0.110
Socialising (+)	41	3.86 (0.88)	25	3.84 (0.86)	16	3.90 (0.96)	0.836	-0.034
Financial problems (-)	42	1.74 (0.91)	25	1.71 (0.82)	17	1.78 (1.05)	0.766	-0.048
Siblings (-)	39	2.22 (1.04)	23	2.34 (1.06)	16	2.03 (1.01)	0.304	-0.167
Relationship status	40	<u>N</u>	24	<u>N</u>	16	<u>N</u>	0.037	
Single		28		20		8		
Partner		12		4		8		

Note: Effect size r is calculated for intellectual functioning, intrusive imagery, and social functioning variables, and partial eta squared is used for psychological functioning (+) higher scores indicate positive impact, (-) higher scores indicate negative impact

*Ns are different due to missing data, non-applicability, and/or excluded cases

^aCompared to population norms

^bUsing cut-off score of 10 points

with CRT reported more cancer-related images than controls, although this difference was not statistically significant, $L\chi^2(1) = 4.13, p = 0.069$.

Social functioning

IOC-CS scores. There were no differences detected between participants who received CRT compared to participants who received RT elsewhere in the body for eight of the nine IOC-CS variables, as summarised in Table 2 (all $p > 0.025$). However, participants who received CRT reported greater problems with memory and thinking ($Mdn = 3.00$) than the controls ($Mdn = 2.20$), $U = 112.0, z = -2.59, p = 0.009$.

Relationship Status. There was a significant association between RT location and relationship status $L\chi^2(1) = 5.06, p = 0.037$, such that the odds of being single were five times higher if participants received CRT rather than RT to the body.

2. Risk Factors

Given that minimal differences were detected between CRT survivors and controls, the groups were combined when exploring risk factors independently.

Time since Treatment

Although greater time since successfully completing treatment appeared to be associated with higher scores on the 'Talking with Parents' subscale of the IOC-CS, this correlation was not significant at the corrected alpha level, $r_s = .32, p = 0.042$.

Time since treatment was not related to any other measure of psychosocial or cognitive functioning (see Table 4; all $p > 0.025$).

Table 4.

Correlations with Time since Treatment and RT Dosage across Domains

	Time Since Treatment	RT Dosage
Intellectual functioning		
IQ	-.057	-.406**
Psychological functioning		
Depression	-.064	.094
Anxiety	.003	-.235
Intrusive Imagery		
Total number of images	-.187	.097
Emotions (max. 100)	.128	.091
Vividness (max. 100)	.071	-.077
Nowness (max. 100)	-.024	.065
Sensory (max. 100)	.273	-.023
Type of images reported	.139	.254
Social functioning		
Life challenges (-)	.013	-.093
Body and health (+)	.073	.042
Talking with parents (+)	.315*	-.037
Personal growth (+)	-.100	-.078
Memory and thinking (-)	-.212	-.007
Health literacy (+)	.128	-.010
Socialising (+)	.109	-.044
Financial problems (-)	.100	-.086
Siblings (-)	-.128	-.099
Relationship status	.200	

*** $p < 0.01$, ** $p < 0.025$, * $p < 0.05$

(+) higher scores indicate positive impact, (-) higher scores indicate negative impact

RT Dosage

Across all participants, the total RT dosage received was significantly correlated with IQ, $r_s = -.41$, $p = 0.013$ such that participants who received greater doses of RT to any part of the body achieved lower IQ scores. RT dosage was not significantly related to any measure of intrusive imagery, or psychological or social functioning (see Table 4; all $p > 0.025$).

Additional Treatments

Table 5 presents mean scores and p -values of test scores comparing participants who received additional chemotherapy (vs no chemotherapy) and participants who received surgery (vs no surgery).

Chemotherapy

Survivors who received chemotherapy did not differ from those who did not receive chemotherapy across all the explored domains of functioning (all $p > 0.05$).

Surgery

Using MANOVA and Pillai's trace, there was an overall effect of surgery on psychological functioning, $V = 0.27$, $F(2, 39) = 7.24$, $p = 0.002$. However, separate univariate analyses revealed surgery only had a significant effect on anxiety, $F(1, 40) = 6.49$, $p = 0.015$, such that participants who did not have surgery reported greater anxiety than those who did. Having surgery did not significantly affect self-reported depression, $F(1, 40) = 0.51$, $p = 0.48$. There were no other differences between surgery and no-surgery groups on measures of cognitive or social functioning (all $p > 0.05$).

3. Associations between Risk Factors

After each risk factor was evaluated independently, significant findings were explored further using regression analysis. When analysing the risk factors in isolation, RT dosage was found to be correlated with IQ, and anxiety was significantly different across surgery groups. Accordingly, regression analyses were conducted to explore the predictive effects of proposed risk factors on IQ and

Table 5.

Mean Scores, p-values, and Effect Sizes for Significant Differences between Additional Treatment Groups

	N*	Chemotherapy Mean (SD)	N*	No Chemotherapy Mean (SD)	p- value	Effect size		N*	Surgery Mean (SD)	N*	No Surgery Mean (SD)	p- value	Effect size	
						<i>r</i>	η^2						<i>r</i>	η^2
Intellectual functioning IQ	32	102.2 (11.5)	10	108.8 (11.2)	0.117	0.245		24	102.5 (12.9)	18	105.3 (9.9)	0.45	0.12	
Psychological functioning	32	6.63 (4.74)	10	6.50 (4.93)	0.929		0.004	24	6.88 (4.59)	18	6.22 (5.00)	0.002		0.271
Depression	32	5.31 (3.80)	10	6.00 (5.20)	0.927		0.001	24	4.25 (3.74)	18	7.11 (4.11)	0.481		0.013
Anxiety					0.787		0.002					0.015		0.140
Intrusive Imagery														
Total number of images	32	11.4 (12.9)	8	8.5 (10.3)	0.418	-0.035		23	11.9 (12.6)	17	9.4 (12.2)	0.409	-0.133	
Emotions (max. 100)	28	73.0 (26.9)	7	70.0 (14.1)	0.455	-0.130		21	72.6 (25.3)	14	72.1 (24.8)	0.992	-0.001	
Vividness (max. 100)	28	75.6 (25.3)	7	56.4 (35.4)	0.115	-0.210		21	69.5 (30.5)	14	75.2 (24.8)	0.656	-0.078	
Nowness (max. 100)	28	47.5 (34.9)	7	47.1 (36.4)	0.960	-0.010		21	45.7 (36.2)	14	50.0 (33.3)	0.695	-0.069	
Sensory (max. 100)	27	88.3 (17.0)	7	83.6 (30.0)	0.817	-0.043		21	86.0 (24.4)	14	83.2 (24.9)	0.939	-0.015	
Type of images reported	32	<u>N</u>	10	<u>N</u>	0.178			24	<u>N</u>	18	<u>N</u>	0.262		
No images reported		4		1					2		3			
Non-cancer related		23		5					15		13			
At least one cancer- related		5		4					7		2			

Social functioning												
Life challenges (-)	32	2.06 (0.63)	10	2.60 (0.96)	0.091	-0.262	24	2.26 (0.85)	18	2.11 (0.59)	0.692	-0.063
Body and health (+)	32	3.25 (0.81)	10	3.14 (0.75)	0.615	-0.080	24	3.29 (0.81)	18	3.13 (0.77)	0.508	-0.104
Talking with parents (+)	32	3.89 (1.04)	10	3.70 (1.45)	0.830	-0.035	24	3.93 (1.23)	18	3.74 (1.02)	0.352	-0.145
Personal growth (+)	32	3.44 (0.91)	10	3.40 (1.12)	0.901	-0.021	24	3.35 (0.99)	18	3.55 (0.90)	0.645	-0.072
Memory and thinking (-)	32	2.78 (0.95)	10	2.78 (0.84)	0.994	-0.001	24	2.89 (0.99)	18	2.62 (0.81)	0.483	-0.110
Health literacy (+)	30	3.97 (0.71)	10	3.60 (0.59)	0.112	-0.253	23	4.01 (0.73)	17	3.71 (0.62)	0.156	-0.226
Socialising (+)	31	3.87 (0.86)	10	3.83 (1.01)	0.982	-0.001	23	3.88 (0.95)	18	3.83 (0.82)	0.650	-0.073
Financial problems (-)	32	1.78 (0.87)	10	1.60 (1.06)	0.324	-0.155	24	1.63 (0.70)	18	1.89 (1.14)	0.777	-0.045
Siblings (-)	31	2.26 (1.13)	8	2.06 (0.56)	0.995	-0.001	23	2.18 (1.11)	17	2.26 (0.97)	0.643	-0.076
Relationship status	30	<u>N</u>	10	<u>N</u>	0.139		24	<u>N</u>	17	<u>N</u>	0.296	
Single		19		9				18		10		
Partner		11		1				5		7		

Note: Effect size r is calculated for intellectual functioning, intrusive imagery, and social functioning variables, and partial eta squared is used for psychological functioning

(+) higher scores indicate positive impact, (-) higher scores indicate negative impact

*Ns are different due to missing data, non-applicability, and/or excluded cases

^aCompared to population norms

^bUsing cut-off score of 10 points

anxiety. Two hierarchical regression analyses were completed for IQ and anxiety, to test the effects of risk factors after controlling for RT treatment group (CRT vs control). It was necessary to control for RT treatment group because previous analysis showed that CRT and control groups differed in terms of RT dosage and use of concurrent chemotherapy. RT treatment group (CRT vs controls) was entered at step one and RT dosage, chemotherapy, and surgery added simultaneously on a second step. Time since treatment was not included as it was found to be comparable across CRT and control groups, and no associations with either IQ or anxiety were identified.

IQ

RT treatment group (CRT vs control) did not significantly predict IQ scores at step one, $R^2 = 0.004$, $F(1, 35) = 0.14$, $p = 0.709$. Introducing the risk factors at step two explained a significantly greater proportion of the variance in IQ ($\Delta R^2 = 0.220$, $p = 0.044$), and when all four variables were included in the model, the cumulative variance in IQ accounted for was 22.4%. Although the overall model was not significant at step two, $R^2 = 0.224$, $F(4, 32) = 2.31$, $p = 0.079$, both RT dosage and chemotherapy were found to be significant predictors of IQ (see Table 6).

In interpreting this regression analysis and assessing multicollinearity, findings of preliminary analyses were considered, which identified differences in RT dosage between CRT and control groups, and surgery and no-surgery groups. Although correlations between RT dosage, and RT treatment group, $r = .45$, $p = 0.002$, and surgery group, $r = 0.60$, $p < 0.001$ were found, tests of multicollinearity indicated that only a low level was present ($VIF = 1.33$ for RT treatment group, $VIF = 1.83$ for

RT dosage, $VIF = 1.56$ for surgery, $VIF = 1.14$ for chemotherapy). Results therefore suggest that RT dosage and chemotherapy are independent predictors, the effects of which cannot be accounted for by RT treatment group.

Table 6.

Multiple Regression Analysis of Factors Predicting IQ Scores

	B	SE B	β	t	p
Step 1					
Constant	104.81	3.06			
RT Treatment Group	-1.53	1.06	-.06	-0.38	0.709
Step 2					
Constant	136.05	11.23			
RT Treatment Group	0.33	4.33	.01	-0.08	0.941
RT Dosage	-0.53	0.24	-.46	-2.16	0.038
Chemotherapy	-10.18	4.81	-.35	-2.11	0.042
Surgery	1.32	4.72	.05	0.28	0.782

Note: $R^2 = .004$ for Step 1, $\Delta R^2 = .220$ for Step 2 ($p = 0.044$); significant p -values highlighted in bold

These findings were further explored with an additional hierarchical regression which aimed to clarify whether the identified predictors of RT dosage and chemotherapy had additive or multiplicative effects on IQ. RT treatment group (CRT vs controls) was entered at step one, with RT dosage and chemotherapy added simultaneously on a second step, and a further interaction variable of RT dosage multiplied by chemotherapy (RT dosage x chemotherapy) added on a third step (see Table 7). RT dosage and chemotherapy variables were centered before multiplying to reduce multicollinearity, which was found to be low across the model ($VIF = 1.34$ for RT treatment group, $VIF = 3.90$ for RT dosage, $VIF = 3.27$ for chemotherapy, $VIF = 4.47$ for RT dosage x chemotherapy). Although RT dosage and chemotherapy remained significant independent predictors of IQ, there was no evidence of an interaction between the two variables, as shown in Table 7.

Table 7.

Multiple Regression Analysis of Factors and Interactions Predicting IQ Scores

	B	SE B	β	t	p
Step 1					
Constant	104.81	3.06			
RT Treatment Group	-1.53	1.06	-.06	-0.38	0.709
Step 2					
Constant	135.1	10.51			
RT Treatment Group	0.33	4.27	.01	0.08	0.938
RT Dosage	-0.49	0.20	-.42	-2.43	0.021
Chemotherapy	-10.19	4.75	-.35	-2.15	0.039
Step 3					
Constant	167.30	22.11			
RT Treatment Group	0.75	4.17	.03	0.18	0.859
RT Dosage	-0.95	0.34	-.82	-2.78	0.009
Chemotherapy	-20.60	7.84	-.71	-2.63	0.013
RT Dosage x Chemotherapy	2.09	1.27	.52	1.65	0.110

Note: $R^2 = .004$ for Step 1, $\Delta R^2 = 0.218$ for Step 2 ($p = 0.017$), $\Delta R^2 = 0.061$ for Step 3 ($p = 0.110$); significant p -values highlighted in bold

Anxiety

RT treatment group did not significantly predict anxiety scores at step one, $R^2 = 0.037$, $F(1, 35) = 1.34$, $p = 0.256$, and the model remained non-significant after adding risk factors at step two, $R^2 = 0.112$, $F(4, 32) = 1.01$, $p = 0.415$. Furthermore, none of the risk factors significantly predicted anxiety scores, as shown in Table 8, indicating that surgery may not be a significant risk factor in later anxiety when considered alongside other risk factors.

Table 8.

Multiple Regression Analysis of Factors Predicting Anxiety

	B	SE B	β	t	p
Step 1					
Constant	6.06	0.94			
CRT or controls	-1.44	1.25	-.19	-1.16	.256
Step 2					
Constant	3.58	3.76			
CRT or controls	-1.05	1.45	-.14	-0.73	0.474
RT Dosage	0.06	0.08	.16	0.72	0.478
Chemotherapy	1.10	1.61	.12	0.68	0.680
Surgery	-2.35	1.58	-.31	-1.48	0.148

Note: $R^2 = .037$ for Step 1, $\Delta R^2 = .076$ for Step 2 ($p = 0.448$); significant p -values highlighted in bold

Discussion

The aim of the current study was to provide a preliminary overview of how receiving radiotherapy to the brain during adolescence affects multiple domains of functioning in adulthood. The impact of additional, potentially confounding, risk factors and the relationships between them were also examined. Key findings are discussed in order of the research questions.

Late effects associated with CRT

In examining the primary research question, which asked how late effects differed for survivors treated with CRT (to the brain) and a control group of survivors treated with non-CNS RT elsewhere in the body, few differences were found between the groups. Overall, results from all survivors were comparable to the normal population; all participants were found to have IQs within the normal range, and the proportion of participants reporting significant depression or anxiety was within expected limits.

Furthermore, responses on a measure of social functioning suggested generally positive adjustments to cancer, and minimal ongoing negative experiences.

Nevertheless, significant differences between the CRT group and controls were found in self-reported memory functioning, and relationship status.

Several explanations are considered in reviewing the finding that the majority of participants did not demonstrate significant late effects across domains. The current study's failure to identify differences between CRT and control groups may reflect the fact that older age at the time of irradiation is protective, such that minimal adverse effects are experienced in adulthood. This explanation is consistent with the paediatric literature, which posits that younger children (typically younger than seven years) are more vulnerable to the damaging effects of CRT (e.g. Mulhern, Hancock, Fairclough, & Kun, 1992; Robinson et al., 2013; Roman & Sperduto, 1995). It is also supported by studies exploring post-traumatic growth, which suggest that many survivors of adolescent cancer are not negatively affected, and in fact, experience increased resilience and psychological growth after successfully completing cancer treatment (Barakat, Alderfer, & Kazak, 2006; Greup et al., 2018).

However, it is not possible to definitively conclude from this data that CRT in adolescence results in minimal neurocognitive or psychosocial impairment, for several important reasons. Firstly, the lack of observed intellectual impairment does not rule out the possibility that some decline may have already occurred in other areas of neurocognitive functioning. Given that CRT is proposed to predominantly damage white matter and subcortical structures (Corn et al., 1994; Reddick et al., 2000; Scantlebury et al., 2016), and IQ tests primarily measure posterior association

cortex integrity (Lezak, 2012), the brief measure of intellectual functioning used in the present study may not have been sufficiently sensitive to CRT-induced damage. Several studies of older children treated with CRT using alternative measures have revealed mild to moderate deficits in memory, attention, verbal learning, novel problem-solving, and processing speed (e.g. Armstrong et al., 2004; Kiehna, Mulhern, Li, Xiong, & Merchant, 2006; Mulhern et al., 2004), even in the presence of average IQ (Packer et al., 1989). Secondly, even if no deficits are present in other areas, it is possible that decline may occur in the future, in IQ or other neurocognitive functions (see discussion of time since treatment in ‘Risk Factors’). Thirdly, this null finding may instead represent a problem with statistical power as the relatively small sample size limited the ability of the current study to detect smaller effects.

Differences between CRT and control groups

Despite most measures suggesting normal functioning across both groups, participants treated with CRT reported significantly greater problems with memory, and were five times more likely than controls to be single.

The first finding is consistent with those of Ellenberg et al. (2009) and Armstrong et al. (2010) who found that a similar group of survivors of CNS malignancies within the Childhood Cancer Survivor Study, treated with total or partial brain irradiation, reported greater impairment on memory factors than non-CNS cancer survivors and siblings. On the basis of these researchers’ conclusions, it seems possible that self-reported memory problems in the CRT group may reflect genuine memory problems not present in controls, which were not measured by the current study. However, further research examining the association of self-reported cognition with objective

performance has mostly failed to find a relationship, and instead suggests that subjective perception of cognition represents a separate construct, more closely related to psychological distress (Li, Root, Atkinson, & Ahles, 2016; Marino et al., 2009; Skaali et al., 2011). Although there were no significant differences observed between the groups in depression or anxiety, there was a trend for more of the intrusive images reported by CRT-treated brain tumour survivors to be cancer-related than those reported by survivors of other cancers, which may indicate increased distress and/or preoccupation with cancer in this group that remained non-significant in the context of small sample size and low statistical power.

Regarding the second finding, previous studies have found that survivors of CNS tumours, particularly those treated with CRT, are less likely to marry and/or form intimate relationships than other cancer survivors and healthy peers, owing to the impact of CRT on cognitive functioning (Frobisher, Lancashire, Winter, Jenkinson, & Hawkins, 2007; Koch et al., 2011; Langeveld et al., 2003). Although relationship status was significantly different between CRT and controls in the present study, indicating a specific effect of CRT above and beyond the experience of having cancer during adolescence, there were no differences observed in IQ, suggesting that this difference was not mediated by intellectual functioning. It is possible, however, that this finding may be explained by deficits in other cognitive functions not measured in the present study.

Risk factors

Time since treatment

Results suggested no significant effects of time since treatment, which ranged from two to 14 years across all participants. Regarding neurocognitive outcomes, this finding may again point to a protective effect of treatment during adolescence, consistent with studies of survivors of childhood cancer which found that IQ declines over time were only observed in survivors who were younger when irradiated (Hoppe-Hirsch et al., 1990; Mulhern et al., 1992; Mulhern et al., 2001; Ris et al., 2001). However, the potential effects of time since CRT treatment on cognition may also have been masked by the sole use of IQ measures. Longitudinal studies measuring multiple neurocognitive abilities suggest that progressive declines in IQ may actually be driven by deficits in other neurocognitive processes, such as processing speed, attention, and working memory, which precede deficits in intelligence (Krull et al., 2013; Schatz, Kramer, Ablin, & Matthay, 2000). Furthermore, Harila et al. (2009) found that whilst both irradiated and non-irradiated cancer survivors experienced mild declines over the five years following treatment, only irradiated survivors showed further decline leading to impairment 20 years after diagnosis. It is therefore possible that deficits in IQ were yet to emerge in the present sample of CRT survivors, who participated an average of 6.8 years after treatment completion.

Additionally, whilst the follow-up interval may have been too early to detect IQ impairment in this sample, it may have been too late to detect psychosocial problems. Stam and colleagues (2005) measured ‘course of life’ in 353 Dutch young adult survivors of childhood cancers, and found that, although some participants achieved

fewer overall social and psychosexual milestones than healthy peers, others simply achieved them at later ages. Similar patterns have also been observed in educational and vocational outcomes (Dieluweit et al., 2011; Koch, Kejs, Engholm, Johansen, & Schmiegelow, 2004). It is therefore also possible that participants initially experienced a hampered course of life, but had caught up to peers by the point of participation.

Chemotherapy

Although no differences were detected between participants who received chemotherapy and those who did not when risk factors were evaluated independently, regression analysis performed to assess each risk factor whilst controlling for the RT treatment group (CRT vs controls) indicated that receiving chemotherapy in addition to any type of RT was significantly predictive of lower IQ scores. The simplest interpretation of this finding is that the higher the number of treatment modalities received, the greater CNS risk is incurred (Mulhern, Crisco, & Kun, 1983), however, additional surgery was not found to affect IQ. It is also possible that additional chemotherapy is administered for more extensive or aggressive cancers, thus the cancer itself may also have greater adverse effects on IQ (Wassenberg, Bromberg, Witkamp, Terhaard, & Taphoorn, 2001).

Another explanation of this finding is that radiotherapy interacts with chemotherapy in specific ways that potentiate its toxic effects on brain integrity, exceeding those of either radiotherapy or chemotherapy alone. Specifically, CRT is proposed to disrupt the blood-brain barrier, increasing the concentration of chemotherapeutic agents in the brain (Deangelis et al., 1992; Wen, 2003). Intrathecal chemotherapy especially,

which delivers chemotherapy directly into the cerebrospinal fluid surrounding the brain and spinal cord, has been implicated in studies of childhood cancer survivors, as being consistently neurotoxic when administered adjuvantly with RT (Armstrong et al., 2004; Bleyer et al., 1990; Brown et al., 1992; Duffner, 2004; Peterson et al., 2008). The present results suggest an additive effect of RT and chemotherapy, such that subsequent IQ scores are lower if treated with both modalities. Given that all participants received RT, it was not possible to test whether RT (of any dosage) and chemotherapy have multiplicative effects on IQ. However, regression analysis revealed that RT dosage and chemotherapy did not interact in their effects on IQ, suggesting that chemotherapy does not have a more adverse impact when combined with higher RT doses, and may have similar effects at lower doses.

RT dosage

Perhaps the most unexpected finding was that RT dosage also significantly predicted IQ, independently of where RT was administered in the body. In comparison to the relative wealth of studies which identify adverse neurocognitive outcomes in survivors of CNS malignancies treated with CRT, research on neurocognitive effects of non-CNS RT in other cancers is limited, even within the paediatric literature. When studied as a mixed group of non-CNS malignancy survivors, levels of neurocognitive impairment have not exceeded that of healthy sibling controls, and cognition has therefore been presumed to be unaffected by non-CNS RT (Ellenberg et al., 2009). However, examination of specific non-CNS cancer diagnoses and treatment protocols reveals a different picture. Specifically, mediastinal RT (to the central compartment of the thoracic cavity) administered in the treatment of

Hodgkin's lymphoma is suggested to be related to neurocognitive dysfunction due to its effects on cardiovascular health (Krull et al., 2012; Prasad, 2013).

Despite a multitude of studies documenting the existence of neurotoxicity following CRT and its effects on white matter, it remains that little is known about the precise mechanisms underpinning the development of dysfunction. Classically, two hypotheses have been suggested; in the glial hypotheses, oligodendrocytes (myelinating cells) are proposed to be especially vulnerable to irradiation, resulting in demyelination (Monje & Palmer, 2003). Alternatively, the vascular hypothesis states that injury induced by RT leads to vascular ischaemia and infarction, which in turn, leads to white matter necrosis (Pereira-Dias et al., 2014). It is possible that the cardiac complications induced by mediastinal RT in Hodgkin's lymphoma affect white matter and neurocognitive functioning in turn, consistent with the vascular hypothesis. Research with coronary heart disease patients supports this conclusion as multifocal white matter lesions have been identified on magnetic resonance imaging in this population (Jeerakathil et al., 2004), alongside problems with processing speed, memory, attention, and executive functions (Debette et al., 2007). Moreover, this association is suggested to be dose-dependent; whilst low doses of RT (15-30Gy) may result in some damage to coronary circulation, higher doses (40-45Gy) have been associated with early latency for fatal ischaemic disease (Hancock, Donaldson, & Hoppe, 1993; Mulrooney et al., 2010).

Although the exact mechanisms remain unclear, it is conceivable that individuals treated with CRT and individuals treated with non-CNS RT for Hodgkin's lymphoma may experience similar levels of neurotoxicity following RT in a dose-

dependent manner, as specified by the glial and vascular hypotheses, respectively. Given that a large proportion (44%) of the control group in the present study was comprised of Hodgkin's lymphoma survivors, it is unsurprising that an effect of RT dosage was identified independently of RT treatment group (CRT vs non-CNS controls). This subgroup of control participants may also further explain the apparent lack of differences between groups across other domains of functioning.

Implications and future directions

If it is assumed that the present sample is representative of the existing population of adult survivors of adolescent cancers, there are several important theoretical and clinical implications.

Although the observed lack of impairment in the current sample does not allow the acceptance of the null hypothesis, if it is true that individuals treated during adolescence experience minimal adverse late effects in adulthood, this would have significant implications for the proposed mechanisms of CRT-induced damage. Despite undergoing another period of neural plasticity in adolescence, current findings could suggest that the effects of CRT are specific to the changes occurring in the brain during childhood. For example, CRT may affect the process of myelin synthesis or cause permanent damage to myelinating glial cells that are expected to have matured by adolescence (Monje & Palmer, 2003). This hypothesis is supported by a longitudinal structural imaging study of medulloblastoma survivors treated with CRT which found that survivors who were aged below 12 at the time of irradiation showed successive decreases of white matter volume of -1.1% per year, whilst survivors who were older than 12 years at the time of irradiation showed white matter growth at a comparable rate to healthy controls (Reddick et al., 2000). It is

further supported by the relatively few and benign intrusive images reported by the majority of participants in the present study, as this may suggest that at least one aspect of hippocampal functioning remains unaffected by CRT in adolescence, even at higher doses. Consequently, it is possible that the significant changes in the brain during this period do not confer increased vulnerability, and adolescence may, in fact, constitute a period of relative resilience to the effects of CRT. However, given the significant limitations of the current study, this conclusion and the associated implications should be interpreted with great caution. Extensive future research is required, with a larger sample of young adult survivors of adolescent cancers and a more diverse range of measures, to clarify whether adult survivors treated in adolescence experience a true protective effect of age, or whether the current results are reflective of the study's limited methodology and/or statistical power.

Secondly, the identified worse effects of higher CRT doses and the greater combined impact of CRT and chemotherapy on IQ may have important clinical implications, for example, in choosing or developing treatment protocols for this age group. In an effort to limit neurocognitive dysfunction associated with CRT, recent research has focused on adjusting paediatric treatment protocols by reducing CRT doses and increasing chemotherapy (Shah et al., 2007; Thomas et al., 2000). However, rather than reduce the likelihood of impairment, the present findings suggest that concurrent chemotherapy during adolescence may have an additive effect on later IQ, regardless of RT dosage. Prospective and repeated cognitive assessment should therefore be included in any future trials combining RT and chemotherapy.

Furthermore, both global injury from CRT in brain tumour survivors, and ischaemic vascular damage resulting from RT given to Hodgkin's lymphoma patients have the potential to reduce cognitive reserves, placing survivors at risk for accelerated ageing or early-onset dementia (Armstrong et al., 2013). Although no participants within the present sample showed impairment in IQ (considered as below average), follow up studies and longitudinal prospective studies are needed to elucidate the effects of irradiation in adolescence across the lifespan.

Limitations

Although the main limitations of the present study have already been discussed, including small sample size leading to potential problems with statistical power, and the reliance on IQ as a sole measure of neurocognitive functioning, there are several additional limitations that must be considered. For example, the heterogeneous group of CRT survivors may not all have received equal doses of CRT to the hippocampal region, serving to confound the effects of CRT on intrusive imagery. Participants also received different regimens of RT, for example, some were treated with additional boosts to the primary tumour site, which may also have differing effects on later functioning. Future research aiming to assess hippocampal functioning in this population could address these limitations by examining the associations between similar variables and exact hippocampal volume using volumetric analysis.

Furthermore, the use of unstandardised measures such as the IOC-CS and the intrusive imagery interview could be said to limit the validity of present findings. However, similar intrusive imagery interviews have been used in other studies

examining intrusive cognitions and memories in cancer patients (e.g. Brewin, Watson, McCarthy, Hyman, & Dayson, 1998; Whitaker, Brewin, & Watson, 2008), and despite being in the early stages of development, the IOC-CS is designed specifically for young adult cancer survivors, and may therefore have greater clinical utility.

Additionally, although survivors of non-CNS cancers who received RT elsewhere in the body were chosen to maximise similarities and provide good control, it is possible that the groups did not sufficiently differ on the required factors, as evidenced by the findings. The response rate of 43% across groups may also indicate that individuals who were experiencing poorer outcomes were less likely to participate in the study.

Lastly, an inevitable limitation concerned with using a cross-sectional design is the unavailability of baseline data and premorbid IQ scores. Longitudinal studies of survivors of childhood cancers propose that, although IQ is not often impaired (below average) in adult survivors of childhood cancers, individuals treated with CRT may still have experienced significant declines above survivors who did not receive CRT (Harila et al., 2009; Krull et al., 2013). To further complicate matters, there is also mounting evidence that brain tumour patients suffer some cognitive deficits prior to commencement of any cancer treatment due to the effects of the tumour itself on the brain, which may further confound the effects of CRT (Duffner et al., 1993; Tucha, Smely, Preier, & Lange, 2000; Wassenberg et al., 2001). Furthermore, other risk factors including tumour location (Ellenberg, McComb, Siegel, & Stowe, 1987), and types of chemotherapy known to have greater effects on

cognition, such as intrathecal methotrexate (Cheung & Krull, 2015), were not differentiated in the current study. In sum, larger-scale longitudinal studies are needed to provide sufficient statistical power to evaluate the relative contributions of many risk factors on later functioning, in addition to accounting for baseline problems.

Conclusions

The present study is amongst the first to evaluate the late effects of receiving CRT in adolescence across domains of neurocognitive and psychosocial functioning. Preliminary findings did not detect any adverse outcomes associated with receiving CRT in adolescence, nor was there evidence of significant differences between CRT and control groups across several domains of functioning, except in self-reported memory functioning and relationship status. RT dosage and chemotherapy were identified as significant risk factors for lower IQ, even in survivors of adolescent cancers treated with non-CNS RT, though IQ scores remained within the average range. Whilst these findings could be understood to mean that there is a protective effect of receiving CRT in adolescence, this conclusion may be premature, as it is constrained by statistical and methodological limitations. Long-term follow-up and prospective studies are therefore essential to clarify and extend current findings.

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Part 3: Critical Appraisal

Introduction

The following critical appraisal will first reflect on the theoretical and practical challenges encountered during the process of project development. It will then discuss the methodological limitations inherent in the current research, and more generally in the study of adult survivors of adolescent cancers, before suggesting how these may be addressed in future research. Finally, this appraisal will consider the null findings of the present study and their implications in the context of post-traumatic growth.

Project Development

Choice of topic

In the first year of clinical psychology training, a multitude of potential projects are presented and discussed with students to aid the process of topic selection. One of the projects offered in the early stages of development was titled ‘Radiotherapy to the hippocampus and the impact on intrusive imagery’. This project aimed to extend the revised dual representation theory of post-traumatic stress disorder (PTSD) developed by Brewin and colleagues, through its application to a young cancer population (Brewin, 2001; Brewin, Dalgleish, & Joseph, 1996; Brewin, Gregory, Lipton, & Burgess, 2010).

I was initially attracted to this topic as I felt it combined all three of my long-standing interests in cognitive neuropsychology, health psychology, and working with young people. I was also excited by the idea of advancing a theory, and in particular, one that explores how brain function directly relates to psychological experience. Furthermore, I felt my experiences prior to starting clinical psychology

training of working in a general neuropsychology service and a specialist child anxiety clinic were well-suited to this research project.

Initial project

The rationale and the design of the initial project can be understood through a more thorough explanation of the theory it was designed to advance. The revised dual representation theory of post-traumatic stress disorder (PTSD) specifies the function of the hippocampus in memory encoding and retrieval (Brewin, 2001; Brewin et al., 2010). It proposes two different types of memory representations encoded during a traumatic event; one type of representation is largely supported by the amygdala, the insula, and the dorsal visual stream, and encodes sensory and emotional information in a form similar to how it was originally experienced (S-reps). The other type is reliant on the hippocampus and the ventral visual stream, and abstracts sensory information, along with the spatial and personal context, to provide a coherent narrative to an event (C-reps). In healthy memory, S-reps are retrieved when the associated C-rep is voluntarily activated.

The theory further states that in the presence of extreme stress and/or trauma, S-reps can be strongly encoded and the hippocampus down-regulated. This can lead to later involuntary re-activation of S-reps by associative cues without the corresponding C-reps and contextual information, experienced as flashbacks in PTSD. These highly sensory and emotional images, mediated by the amygdala, often lack temporal context and are described as having a sense of “nowness” (Brewin, 2001; Ehlers & Clark, 2000; Glazer, Mason, King, & Brewin, 2012).

Patients who have undergone radiotherapy were considered an ideal population to test this theory, and the original aim was to recruit one group of participants who had received focal radiotherapy to the hippocampus, and compare them to a control group of participants who received radiotherapy elsewhere in the body. According to the theory, it was hypothesised that direct damage to the hippocampus would result in poorer contextual processing of information and therefore greater “bottom-up” activation of images and memories, similar to the experience of PTSD. Participants would be compared across a range of measures designed to assess specific hippocampal functions, including an intrusive imagery interview and a virtual environment task designed to test allocentric representation (an aspect of spatial memory which involves holding in mind the locations of environmental features relative to each other) (King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002; King, Trinkler, Hartley, Vargha-Khadem, & Burgess, 2004).

Challenges

Once the project had advanced through the stages of a written proposal, the next step was to discuss the project with the team at the adolescent and young adult oncology service within the London hospital at which the project would run. It was through these meetings that several obstacles were encountered, resulting in the need to re-design the project. The main issue that the original project posed was in recruitment; the radio-oncologists at the hospital advised that, although it was theoretically possible to recruit participants who had had radiotherapy to the hippocampal region, there would be relatively few patients meeting the inclusion criteria and those that did would also have received radiotherapy to other regions, thus it would not be

possible to attribute any differences to hippocampal damage specifically. It was mainly for this reason that an alternative emphasis for the project was considered.

Given the recognised paucity of studies evaluating the late effects of radiotherapy in adolescent cancer patients, and that relationships had been already been established between the researchers and the clinical team, it was decided that the project should proceed within this population. Furthermore, it seemed that recruitment was likely to be difficult if constrained to any one region of the brain specifically, as different radiotherapy treatment protocols are prescribed even for the same tumour type (Burnet, Thomas, Burton, & Jefferies, 2004). Consequently, it was decided that the study would keep a broad focus on cranial radiotherapy, compared to radiotherapy elsewhere in the body. Given the preliminary nature of the study, I further chose to explore multiple domains of functioning in the hope of providing an overview of the late effects of CRT when administered in adolescence.

Methodological and Theoretical Limitations

The present research represents a complex area of study, that has been investigated using many different methodologies. There remains no accepted methodology, though several approaches are evaluated in this critical appraisal.

Studying the specific effects of cranial radiotherapy

Despite a large literature investigating the effects of radiotherapy to the brain dating back to the 1980s, there continues to be significant controversy about its damaging effects. This controversy is due, in large part, to the numerous confounding factors affecting both retrospective and prospective studies of patients receiving cranial

radiotherapy (CRT). Although there are clearly both acute and delayed effects of CRT on multiple brain structures, the predictability of developing impairment in any one area is reduced by the additional confounding factors of: age at irradiation; type, volume, and dosage of radiotherapy received; number of fractions total dose is administered in; specific region of brain irradiated; degree of ‘scatter’ incurred by the method of irradiation; additional treatments such as chemotherapy and/or surgery; and the predisposition to neurotoxicity conferred by genetics, the type of cancer, and tumour location in the brain. (Armstrong, Gyato, Awadalla, Lustig, & Tochner, 2004; Duffner, 2004; Duffner, 2010; Mulhern, Hancock, Fairclough, & Kun, 1992; Roman & Sperduto, 1995; Ullrich & Embry, 2012). Furthermore, several of these risk factors are proposed to interact in their effects on later functioning, making it even more difficult to isolate and ‘unpick’ their relative contributions. This overwhelming but by no means exhaustive list goes some way to describing the complexity of conducting research in this area. It also highlights the difficulty all studies face in drawing conclusions about the specific effects of CRT, over and above those of other risk factors. In designing the present study, I was acutely aware of the difficulty in accounting for the afore-mentioned multitude of risk factors, especially in a smaller sample, and therefore chose to focus on two of the most widely-documented (CRT dosage and concurrent treatments), and an additional risk factor relevant to the study of late effects (time since treatment).

Use of control group

Historically, studies investigating the effects of CRT have employed three different types of control group. The first and the most commonly used control group involves comparison to healthy peers. Whilst some studies have made use of unrelated age-

matched community controls (e.g. Ehrhardt et al., 2018; Scantlebury et al., 2016), the differences between these participants and cancer survivors treated with CRT are significant and it is problematic to conclude that any observed differences are due to CRT alone. Other studies have examined siblings or twins to minimise environmental differences (e.g. Armstrong et al., 2010; Gunn et al., 2015; Said, Cousens, Waters, & Stevens, 1989), though these studies mostly assume controls to be unaffected by their sibling's cancer experiences, which may be misleading.

Secondly, many studies have also compared cancer patients treated with CRT to cancer patients treated with different modalities, for example Taylor et al. (2007) compared CRT-treated individuals to those who received surgery, and many studies have compared the effects of CRT and chemotherapy (e.g. Jankovic et al., 1994; Massimo, Wiley, Bonassi, & Caprino, 2006; Precourt et al., 2002). This method often involves the comparison of different types of cancers, for example brain tumour survivors are frequently compared to survivors of non-central nervous system (CNS) malignancies such as solid-tumours and lymphoma treated with protocols that do not affect the brain (Conklin et al., 2012; Lahteenmaki et al., 2001). Although these groups ostensibly have more in common in terms of the experience of cancer diagnosis and treatment and the corresponding disruption to development, these comparisons are also fraught with multiple confounding factors. For example, both surgery and chemotherapy are proposed to affect cognitive functioning, independently of CRT or cancer diagnosis (e.g. Scheibel, Meyers, & Levin, 1996; van Den Bent et al., 2003).

Finally, a small number of studies have compared cancer patients treated with CRT to a control group of individuals diagnosed with other non-malignant chronic diseases such as rheumatoid arthritis, and Crohn's disease (e.g. García-Pérez, Sierrasesumaga, Narbona-García, Calvo-Manuel, & Aguirre-Ventalló, 1994). This design attempts to account for factors associated with being ill, without the additional confounds of other cancer treatments. However, in addition to being practically difficult to organise owing to the need to engage two different healthcare services, chronic diseases such as rheumatoid arthritis have also been associated with cognitive impairment (Meade, Manolios, Cumming, Conaghan, & Katz, 2018). Furthermore, Meade and colleagues (2018) propose that one of the mechanisms responsible for cognitive impairment in rheumatoid arthritis is the use of medications such as methotrexate and corticosteroids, which have also been identified as risk factors for cognitive dysfunction following cancer treatment (Taphoorn & Klein, 2004).

Whilst it seems that no optimal control condition exists, we chose to compare adult survivors of CNS cancers treated with CRT to age-matched survivors of non-CNS cancers in the current study to ensure similar illness experiences. We also attempted to minimise confounding factors by comparing the same treatment (radiotherapy) across different sites, rather than comparing different treatment modalities. In this way, we hoped to observe the specific effects of completing CRT treatment.

Recruiting young adults

The focus on young adult survivors of adolescent cancers in the present study was also accompanied by an inherent set of challenges, namely in recruitment and data

collection. A key obstacle encountered was in establishing contact with potential participants. Given that participants received treatment during adolescence, the contact details recorded on the hospital patient information database were often outdated, or else belonged to their parents. The developmental tasks associated with young adulthood, such as going to university and moving out of the family home, meant that it was often difficult to contact participants using their parental addresses and phone numbers.

Furthermore, once contact was established additional problems arose concerning availability and incentive. Many potential participants were attending college or working full-time, which limited their availability to participate. Geographic location was also a consideration. Consequently, participants were offered a £10 Amazon voucher and payment of travel expenses, and efforts were made to provide evening and weekend appointments and/or arrange times when patients were due to attend other appointments at the hospital. Although these measures taken rectified these problems to an extent, data collection was still affected by high DNA rates, limiting eventual sample size.

Selecting measures

Due to the anticipated difficulties with recruitment, measures were selected to maximise likelihood of participation. Research has suggested that time burden is a factor in participation rates, with greater uptake observed when the burden of commitment is reduced (Newington & Metcalfe, 2014). Therefore, although it is likely that more reliable data would be collected from longer, more detailed, measures, this consideration had to be balanced against participant burden, and it was

decided that data should be collected in a single testing session lasting approximately 90 minutes. Accordingly, in order to fulfil the aims of the study and measure both psychosocial and cognitive late effects, many measures had to be selected with brevity in mind which, regrettably, imposed several limitations.

Future research may prefer to examine the late effects of CRT across only one domain of functioning, to reduce issues of participant burden whilst improving the reliability of findings. For example, if a similar study were to focus on neurocognitive outcomes, it would be prudent to include measures of memory, attention, and processing speed in addition to IQ as these are proposed to be more sensitive to the effects of CRT (Armstrong et al., 2004; Butler et al., 2008; Roman & Sperduto, 1995). Furthermore, the effects of CRT on hippocampal functioning may have been better evaluated by using one of the specialist virtual reality and topographical spatial memory tasks, developed as an alternative to broad spectrum memory tasks (Burgess, Maguire, Amp, Apos, & Keefe, 2002; Hartley et al., 2007; King et al., 2002).

In the present study, an intrusive imagery interview was also administered to evaluate the impact of CRT-induced damage to the hippocampus in lieu of traditional PTSD measures. Estimates of the prevalence of PTSD in adult survivors of childhood or adolescent cancer vary from 0% to 34.8% (Vuotto, Perez, Krull, & Brinkman, 2015). This large range is due, in part, to the varied definitions and methods of assessment of PTSD. Greater than the limitation that few assessment scales have been validated within a cancer survivor population (Bruce, 2006; Tedstone & Tarrier, 2003), is the overarching problem of whether the chronic nature

of cancer diagnosis and treatment can be regarded as a discrete traumatic event necessary for fulfilment of DSM-5 criteria for PTSD (American Psychiatric Association, 2013). Accordingly, many questionnaire measures of PTSD, such as the Impact of Events Scale (IES; Horowitz, Wilner, & Alvarez, 1979), ask respondents to evaluate their current distress related to a specific event. Although some studies have proceeded to use such measures by asking participants to consider their experiences of cancer broadly, this may reduce the validity of the instrument in detecting PTSD. By using an intrusive imagery interview where participants could report any recent naturally-occurring image, the present study was not constrained by the consideration of a specific traumatic event. According to the hypothesis proposed by the revised dual representation theory, any intrusive images (not necessarily cancer-related) may have the potential to be increasingly vivid, and/or accompanied by stronger emotional and sensory associations if the hippocampus has been damaged by CRT.

In terms of social functioning, the IOC-CS was chosen for inclusion within this project to optimise validity, as it purports to measure aspects of long-term survivorship specific to this population; for example, items ask about the impact of having cancer on fertility, body image, thoughts about dying, relationships, and life goals. However, the IOC-CS remains a relatively new measure and therefore, does not yet have established norms (Zebrack, 2009; Zebrack et al., 2010). Many alternative instruments exist that measure social functioning and/or quality of life with established norms, for example, the Pediatric Quality of Life Inventory (PedsQL) is perhaps the most widely used quality of life measure containing a cancer module (Varni, Seid, & Rode, 1999), and the MOS 36-item Short-Form Health Survey (SF-

36) is useful as a broad measure of health status with regard to social and psychological functioning (Ware & Sherbourne, 1992). However, these measures are limited by their ability to generalise to such a specific population of adult survivors of childhood and adolescent cancers. Future research choosing to focus on the social late effects of CRT with this population should weigh up these advantages and disadvantages so as to select appropriate measures with adequate reliability and validity.

The choice to use the PHQ-9 and GAD-7 to assess symptoms of depression and anxiety, respectively, was primarily due to the speed and ease of completion demonstrated by their use as monitoring tools within IAPT services. Other questionnaire measures may also have been appropriate to assess psychological functioning, such as the Hospital Anxiety and Depression Scale (HADS), which aims to assess psychological symptomology independently of common physical symptoms that may be associated with medical conditions such as fatigue or insomnia (Zigmond & Snaith, 1983).

Post-traumatic Growth

From my subjective experiences of meeting with young adult cancer survivors and discussing their experiences of diagnosis, treatment, recovery, and survivorship, my overall impression was one of resilience and positivity. As the project progressed, and I became increasingly inspired by the attitudes and adaptive skills of this population, I began to consider the concept of ‘post-traumatic growth’. Although not formally measured through qualitative or quantitative means in the present study, it seemed to me that the majority of participants had positively integrated their cancer

experiences with their sense of identity and ambitions. For example, one participant reported that having cancer had prompted him to become a healthcare professional, and another participant had even published a book about his experiences.

Subsequently, the findings of the present study, specifically, that neither survivors treated with CRT or those treated with radiotherapy elsewhere in the body experienced any significant degree of impairment across the multiple domains evaluated, prompted me to consider the concept of post-traumatic growth in more depth.

Post-traumatic growth (PTG), as originally conceptualised by Tedeschi and Calhoun (1995), refers to the positive changes resulting from the struggle through a life-altering experience. A growing literature exists exploring the PTG processes amongst survivors of childhood and adolescent cancers, which suggests that a significant proportion of cancer survivors experience a degree of positive adaptation (Husson et al., 2017). Age at the time of cancer diagnosis is also proposed to be related to PTG, such that older children and adolescents report greater PTG during survivorship (Barakat, Alderfer, & Kazak, 2006). This may suggest that participants in the current study did not report impairment due to increased PTG. However, there is ongoing debate regarding the relationship between PTG and adverse outcomes. Specifically, the association between PTG and post-traumatic stress (PTS) has been well-described in a review by Meyerson and colleagues (2011); whilst some studies have claimed that PTG may buffer the effects of PTS, the majority have conversely found that PTG and PTS are positively related (e.g. Frazier, Tashiro, Berman, Steger, & Long, 2004), indicating that cancer survivors may experience high levels of both (e.g. Barakat et al., 2006; Kilmer & Gil-Rivas, 2010). Further studies of adult

survivors of adolescent cancers treated with CRT could explore PTG formally as this knowledge may have important clinical implications for the specialist late effects services designed for this population.

Conclusions

It is important to recognise the many complexities and challenges inherent in the study of the late effects of CRT and in conducting research with a young adult cancer survivor population. Despite careful consideration of these factors within the present study, even leading to a re-design in the initial stages, there remain significant methodological and theoretical limitations which constrain the subsequent conclusions. Nevertheless, the current findings have merit in establishing a basis upon which future research into the late effects of receiving CRT in adolescence can build. Although research on life-altering events has typically focused on the negative sequelae of these experiences, it is further hoped that future studies can integrate indices of post-traumatic growth alongside the measurement of adverse neurocognitive and/or psychosocial outcomes.

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Appendices

Appendix A: Invitation Letter

Name
Address Line 1
Address Line 2
Postcode

Dear Patient,

We are writing to invite you to be part of an important new study taking place within the Teenage and Young Adult Psycho-oncology Service. We are trying to understand better what it is like to undergo and recover from cancer treatment as a young adult. The results could go towards designing future interventions to help young people through the difficult process of diagnosis, treatment and recovery. We are recruiting participants between the ages of 18 and 25, who completed cancer treatment at least two years ago. **Please read the enclosed information sheet carefully**, which contains all the important information about the research.

Dr Daniel Glazer, Senior Clinical Psychologist, and Professor Chris Brewin, Professor of Clinical Psychology, are overseeing the project conducted by Lara Payne as part of a Doctorate in Clinical Psychology at University College London.

If you are interested in participating in this research, either email us on lara.payne1@nhs.net or daniel.glazer@uclh.ac.uk **OR** complete and return the tear-off slip at the bottom of this letter to the below address.

*Dr Daniel Glazer and Lara Payne
Department of Child & Adolescent Psychological Medicine
Paediatric & Adolescent Division
University College Hospital
235 Euston Road
London
NW1 2BU*

You will also receive a telephone call from us in the next 2-4 weeks where you will be given the opportunity to ask any questions you might have. We will then schedule a one-off visit to the UCH Macmillan Cancer Centre for you to participate. We will try to arrange your participation in this study to coincide with another hospital appointment where possible, to minimise any inconvenience for you.

Thank you for your participation in this research.

Participant Invitation Letter, IRAS Number: 224626, Version 2, 18/08/17



University
College
Hospital

National Hospital
for Neurology and
Neurosurgery

Eastman
Dental
Hospital

Royal National
Throat, Nose
and Ear Hospital

Heart
Hospital

Royal London
Hospital for
Integrated Medicine

Yours sincerely,

Teenage and Young Adult Psycho-Oncology Service
UCLH

PARTICIPATION SLIP

Dear Researcher Team at the Teenage and Young Adult Psycho-oncology Service,

I wish to participate in the study described in the attached letter and information sheet.

PATIENT FULL NAME: _____

PATIENT CONTACT NUMBER: _____

PATIENT SIGNATURE: _____

Participant Invitation Letter, IRAS Number: 224626, Version 2, 18/08/17

uclh

University
College
Hospital

National Hospital
for Neurology and
Neurosurgery

Eastman
Dental
Hospital

Royal National
Throat, Nose
and Ear Hospital

Heart
Hospital

Royal London
Hospital for
Integrated Medicine

Appendix B: Participant Information Sheet

Young Adult Cancer Survivors' Views about their Quality of Life



We would like to invite you to participate in a new research study, which looks at the effects of receiving radiotherapy as a young adult in later life.

Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. You are welcome to talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part.
Part 2 gives you more detailed information about the conduct of the study.

Please ask us if there is anything that is not clear. Take time to decide whether or not you wish to take part.

PART 1

What is the purpose of the study?

To date, a lot of cancer research focuses on either adults or children, with little attention paid to the experiences of adolescents and young adults. We wish to learn more about the effects of having different types of cancers in young adulthood at least two years after treatment is completed. By obtaining the insights of people who have been through cancer diagnosis, treatment, and recovery can we begin to design better treatments for people like you who will go through radiotherapy in the future.

Why have I been invited?

We are recruiting participants between the ages of 18 and 30, who completed cancer treatment two years ago or more. We are keen to hear from you about your experience of having radiotherapy treatment when you were younger, and all the different ways it affected your life. This will be different for everyone so we are hoping that lots of people will take part to help us build a more detailed picture of what it is like to have cancer whilst in the (sometimes difficult) process of becoming an adult.

Do I have to take part?

It is up to you whether you would like to participate in this research. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important to read the information on this sheet carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information.

If you wish to participate, simply return the response slip to the address provided OR email us on lara.payne1@nhs.net or daniel.glazer@nhs.net to let us know that you would like to be involved.

What will happen to me if I take part?

We will invite you for a one-off meeting, lasting approximately 1.5 hours. You will be provided with breaks as needed.

Are there any expenses or payments involved?

We will endeavour to arrange appointments at a time when you might be visiting the hospital for a review appointment. Where this is not possible and you will have to make a special trip, we will reimburse your travel costs in getting to the UCH Macmillan Cancer Centre if you can provide receipts for your journey. We will also provide every participant with £10 Amazon voucher in return for their time.

What will I have to do?

We will telephone you within the 2-4 weeks to answer any questions you might have about the research. If you would like to participate, we will arrange a time for you to visit to the UCH Macmillan Cancer Centre. During this visit, you will be asked to carry out some short tasks and puzzles that look at your general abilities. You will also be asked some questions on your daily experiences of mental imagery and there will be some questionnaires to fill in that ask about mood, and your social life.

What are the possible disadvantages and risks of taking part?

There is a small chance that you may feel distressed answering some of the questions or filling in the questionnaires. If this distress continues and you would like additional support then we recommend that you contact your GP or Dr Daniel Glazer, Clinical Psychologist within the Teenage and Young Adult Oncology Service.

What are the possible benefits of taking part?

You may find the project interesting and, once the research is complete, it could provide some useful information about how having radiotherapy affects young people. Although we cannot promise this study will help you, the information we get from this study may go towards designing better treatments for people like you who will go through radiotherapy in the future.

What happens after the research study stops?

At the end of the study, we may email you with a summary of our overall findings if this would be of interest to you – we will ask you whether you would like to receive this information during your visit. We will also obtain a copy of your brain scan, which will be anonymised and retained for use in relevant future research, if you consent to this.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information concerning this is given in Part 2 of this information sheet. If you have any concerns or complaints, you should contact the researcher in the first instance.

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART 2

What will happen if I don't want to carry on with the study?

You may withdraw from the project at any point without giving a reason. A decision to withdraw at any time, or decision not to take part, will not affect any standard of care you receive. If you withdraw from the study, the data you provided will be retained unless you wish for it to be destroyed.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (see contact details below). Every care will be taken in the course of this study. However if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects (adverse events) you may have experienced due to your participation in the clinical trial, the normal National Health Service complaints mechanisms are available to you. Please ask your study doctor if you would like more information on this. Details can also be obtained from the Department of Health website: <http://www.dh.gov.uk>. Alternatively, you can contact the Patient Advice Liaison Services (PALS) at UCLH by email: PALS@uclh.nhs.uk or by telephone: 0203 447 3042.

Will my taking part in this study be kept confidential?

If you consent to take part in this study, the records obtained while you are in this study and your brain scan data will remain strictly confidential at all times. The information will be held securely on paper and electronically at your treating hospital and the main hospital site managing this research under the provisions of the 1998 Data Protection Act. You will be allocated a trial number, which will be used as a code to identify you on all forms and brain scan files. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised. By signing the consent form you agree to this access for the current study and any further research that may be conducted in relation to it, even if you withdraw from the current study.

If you withdraw consent from further study treatment, unless you object, your data and samples will remain on file and will be included in the final study analysis.

In line with the regulations, at the end of the study your data will be securely archived for a minimum of 20 years. Arrangements for confidential destruction will then be made.

What will happen to the results of the research study?

The results of the study will be available after it finishes and will usually be published in a journal or be presented at a scientific conference. The data will be anonymous and none of the patients involved in the trial will be identified in any report or publication.

Should you wish to see the results, or the publication, please inform the researcher after you have participated in the study and give your email address. The researchers will then send you a summary of the results once the study is complete.

Who is organising and funding the research?

This study is sponsored by University College London and will form part of an educational qualification for Lara Payne, who is completing a Doctorate in Clinical Psychology (DClinPsy).

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by the North of Scotland Research Ethics Service..

Further information and Contact Details

You are encouraged to ask any questions you wish, before, during or after your participation. If you have any questions about the study, please speak to the researchers. If you wish to read the research on which this study is based, please ask your researcher. If you require any further information or have any concerns while taking part in the study please contact one of the following people:

Study Psychologist

Dr Daniel Glazer (email: daniel.glazer@nhs.net, tel: 0203 447 9086)

Principal Researcher

Lara Payne (email: lara.payne1@nhs.net)

If you wish to participate, simply return the response slip in the addressed envelope provided OR email us on one of the email addresses above to let us know that you would like to be involved.

You can have more time to think this over if you are at all unsure.

Thank you for taking the time to read this information sheet and to consider this study.

Appendix C: Consent Form

Study Number: 17/0250

Participant Identification Number for this trial:

CONSENT FORM

Study: Young Adult Cancer Survivors' Views about their Quality of Life

Name of Researchers: Professor Chris Brewin, Dr Daniel Glazer, Lara Payne

Please initial box

- | | |
|---|--------------------------|
| 1. I confirm that I have read the information sheet dated 22/08/2017 (version 2.2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. | <input type="checkbox"/> |
| 2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. | <input type="checkbox"/> |
| 3. I understand that relevant sections of my medical notes may be looked at by individuals from UCLH NHS Foundation Trust, where it is relevant to my taking part in this research. All data collected will be anonymised and analysed by individuals from UCL. I give permission for these individuals to have access to my records. | <input type="checkbox"/> |
| 4. (If applicable) I give permission for researchers to access the data from my previous cognitive assessments | <input type="checkbox"/> |
| 5. I give permission for researchers to access the imaging data from my scans (e.g. MRI) and I understand that this information may be kept and used in other research in the future. | <input type="checkbox"/> |
| 6. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. | <input type="checkbox"/> |
| 7. I agree to take part in the above study. | <input type="checkbox"/> |

<hr/>	<hr/>	<hr/>
Name of Participant	Date	Signature
<hr/>	<hr/>	<hr/>
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.
Consent Form, IRAS Number: 224626, Version 2.2, 22/08/17

Appendix D: National Health Service Ethical Approval Letter

North of Scotland Research Ethics Service

Summerfield House
2 Eday Road
Aberdeen
AB15 6RE

Telephone: 01224 558458
Facsimile: 01224 558609
Email: nosres@nhs.net



Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

22 August 2017

Professor Chris Brewin
Research Department of Clinical, Educational and Health Psychology
UCL, 1-19 Torrington Place
LONDON
WC1E 7HB

Dear Professor Brewin

Study title: Investigating the Impact of Radiotherapy to the Brain on Psychosocial Functioning in Young Adult Cancer Survivors
REC reference: 17/NS/0082
IRAS project ID: 224626

Thank you for your letter of 18 August 2017, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering letter on headed paper: HRA Cover Letter		21 July 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only): Insurance Confirmation Letter		6 July 2017
Interview schedules or topic guides for participants: Intrusive Imagery Interview Schedule	1.0	21 July 2017
IRAS Application Form: IRAS Form 28072017	224626/111 3380/37/82	28 July 2017
IRAS Checklist XML: Checklist 21082017		21 August 2017
Letter from Funder: Funding Approval from UCL		26 May 2017
Letters of invitation to participant	2	18 August 2017
REC Response to Provisional Opinion		18 August 2017
Participant Consent Form	1.0	21 July 2017
Participant Information Sheet (PIS)	2	18 August 2017
Referee's report or other scientific critique report: Peer Review UCL	1.0	28 February 2017
Research protocol or project proposal: Authorised Protocol	2	18 August 2017
Summary CV for Chief Investigator (CI): Chris Brewin	1.0	21 July 2017
Summary CV for Stuent: Lara Payne		20 July 2017
Summary CV for Supervisor (student research): Daniel Glazer	1.0	21 July 2017
Validated questionnaire: PHQ-9 Depression Measure		28 July 2017*
Validated questionnaire: GAD-7 Anxiety Measure		28 July 2017*
Validated questionnaire: Impact of Cancer - Childhood Survivors Scale (IOC-CS)		21 August 2017*

* date received

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:

<http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance>

We are pleased to welcome researchers and R & D staff at our RES Committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

17/NS/0082	Please quote this number on all correspondence
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With the Committee's best wishes for the success of this project.

Yours sincerely


Chair

Enclosures: "After ethical review – guidance for researchers" SL-AR2

Copy to:  Joint Research Office, UCL

Appendix E: Health Research Authority Approval Letter

Professor Chris Brewin
UCL
1-19 Torrington Place
London
WC1E 7HB

Email: hra.approval@nhs.net

23 August 2017

Dear Professor Brewin

Letter of HRA Approval

Study title:	Investigating the Impact of Radiotherapy to the Brain on Psychosocial Functioning in Young Adult Cancer Survivors
IRAS project ID:	224626
REC reference:	17/NS/0082
Sponsor	University College London

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details

and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document “*After Ethical Review – guidance for sponsors and investigators*”, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the [HRA website](http://www.hra.nhs.uk), and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the [HRA website](http://www.hra.nhs.uk).

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at <http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/>.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>.

IRAS project ID	224626
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HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

Your IRAS project ID is **224626**. Please quote this on all correspondence.

Yours sincerely,

[REDACTED]

Assessor

Email: hra.approval@nhs.net

Copy to: *Miss Lara Payne, UCL, Student researcher*
[REDACTED] *Joint Research Office, UCL, Sponsor and Lead NHS R&D contact*

IRAS project ID	224626
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Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	Version	Date
Covering letter on headed paper [HRA Cover Letter]		21 July 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Verification of Insurance]		11 July 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance Confirmation Letter]		06 July 2017
Interview schedules or topic guides for participants [Intrusive Imagery Interview Schedule]	1.0	21 July 2017
IRAS Application Form [IRAS Form 28072017]	224626/1113380/37/82	28 July 2017
IRAS Checklist XML [Checklist 21082017]		21 August 2017
Letter from funder [Funding Approval from UCL]		26 May 2017
Letters of invitation to participant	2	18 August 2017
Other [REC Response to Provisional Opinion]		18 August 2017
Participant consent form	2.2	22 August 2017
Participant information sheet (PIS)	2.2	22 August 2017
Referee's report or other scientific critique report [Peer Review UCL]	1.0	28 February 2017
Research protocol or project proposal [Authorised Protocol]	2	18 August 2017
Summary CV for Chief Investigator (CI) [Chris Brewin]	1.0	21 July 2017
Summary CV for student [Lara Payne]		20 July 2017
Summary CV for supervisor (student research) [Daniel Glazer]	1.0	21 July 2017
Validated questionnaire [Impact of Cancer - Childhood Survivors Scale (IOC-CS)]		21 August 2017*
Validated questionnaire [PHQ-9 Depression Measure]		28 July 2017*
Validated questionnaire [GAD-7 Anxiety Measure]		28 July 2017*

* date received

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations, capacity and capability and Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Lara Payne

Email: lara.payne.15@ucl.ac.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	Minor amendments have been made to the PIS/ICF documentation post-REC to ensure conformity to HRA Standards (see appendix A for current documents).
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	This is a non-commercial, single site study taking place in the NHS where the single participating NHS organisation is part of a Joint Research Office (JRO) with the study Sponsor. Therefore, no agreements are expected.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional

Section	HRA Assessment Criteria	Compliant with Standards	Comments
			indemnity provided by their medical defence organisation covers the activities expected of them for this research study
4.3	Financial arrangements assessed	Yes	UCL is providing funding for WAS-II forms, travel expenses and gift vouchers.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	
6.3	Devices – MHRA notice of no objection received	Not Applicable	
6.4	Other regulatory approvals and authorisations received	Not Applicable	

Participating NHS Organisations in England

<i>This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.</i>
<p>This is a non-commercial, single site study. There is one site-type involved in the research. Activities and procedures as described in the protocol will take place at participating NHS organisations.</p> <p>If this study is subsequently extended to other NHS organisation(s) in England, an amendment should be submitted to the HRA, with a Statement of Activities and Schedule of Events for the newly participating NHS organisation(s) in England.</p>

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The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.

This is a single site study where the site is part of a JRO with the Sponsor. The R&D office will confirm to the CI when the study can start.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).

A Principal Investigator (PI) is expected at participating NHS organisations. Sponsor does not expect research staff to undertake any specific or additional training for the research.

GCP training is not a generic training expectation, in line with the [HRA statement on training expectations](#).

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken

No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain an honorary research contract. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance. For research team members only administering questionnaires or surveys, a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

IRAS project ID	224626
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Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.

The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Appendix F: Intrusive Imagery Interview

Intrusive Imagery Interview Schedule

I'm going to ask you some questions on your experience of intrusive imagery. Intrusive images are images that automatically pop into your head. They may consist of memories from the past, represent a fantasy about the future or just be an imaginary scene. Unlike normal thoughts and images that we may conjure up, intrusive images automatically pop into our head and may be difficult to control. Do you have any questions? Do you understand?

1. Can you report any spontaneous intrusive images that have automatically appeared into your mind during the past week? (if no, what about during a typical week?).
2. How many different intrusions did you have?
3. How often did you have intrusions overall? (0 = never, 100 = almost all the time)
4. We are going to explore two of the most frequent intrusions. Can you briefly describe these:
 - 1.
 - 2.
5. Do these intrusions relate to a memory of an event?
6. If so can you describe the events?

Intrusion 1/2

7. How many times over the past week did it occur?

8. Rate from 0 (not at all) to 100 (very much so) the extent to which this intrusive image made you feel sad.
9. Rate from 0 (not at all) to 100 (very much so) the extent to which this intrusive image made you feel happy.
10. Rate from 0 (not at all) to 100 (very much so) the extent to which this intrusive image made you feel guilty.
11. Rate from 0 (not at all) to 100 (very much so) the extent to which this intrusive image made you feel ashamed.
12. Rate from 0 (not at all) to 100 (very much so) the extent to which this intrusive image made you feel angry.
13. Rate from 0 (not at all) to 100 (very much so) the extent to which this intrusive image made you feel anxious.
14. Rate from 0 (not at all) to 100 (very much so) the extent to which this intrusive image made you feel helpless.
15. Rate from 0 (very hazy) to 100 (very clear and vivid) how vivid the intrusive image was.
16. Rate from 0 (not at all) to 100 (very much so) the sense of “nowness” of the intrusive image. (nowness = the extent to which it felt like the image/scene was actually happening in the present)
17. Rate from 0 (not at all) to 100 (very much so) the impact the intrusive image had on daily activities.
18. Rate from 0 (not at all) to 100 (very much so) how uncontrollable the intrusive image was.
19. Rate from 0 (not at all) to 100 (very much so) how much distress the intrusive image caused.

20. Rate from 0 (not at all) to 100 (very much so) the extent to which this intrusive image contained smells
21. Rate from 0 (not at all) to 100 (very much so) the extent to which this intrusive image contained tastes.
22. Rate from 0 (not at all) to 100 (very much so) the extent to which this intrusive image contained sounds.
23. Rate from 0 (not at all) to 100 (very much so) the extent to which this intrusive image contained tactile sensations
24. Rate from 0 (not at all) to 100 (very much so) the extent to which this intrusive image contained visual elements.

Repeat qu's 7-24 for the second intrusion

Appendix G: Impact of Cancer for Childhood Cancer Survivors Scale

YOUR BODY AND YOUR HEALTH

We are interested to know how having had cancer affects your body and your health **NOW**, if at all.

Please mark an ☒ in the one box for each statement that best describes your answer.

	Not at all ▼	A little bit ▼	Somewhat ▼	Quite a bit ▼	Very much ▼
1. I lead a healthy life.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
2. I eat a healthy diet.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
3. I exercise.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
4. I am as healthy as others who have never had cancer.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
5. I worry about my health.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
6. Having had cancer limits my ability to work (including school work).	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
7. It is difficult to know whether to push myself physically or to be careful and rest.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
8. I believe I am an attractive person.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
9. I like the way my body looks.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
10. I wear clothing to cover up parts of my body I don't want others to see.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
11. Visible signs of my cancer (scars, braces, prosthesis) make me feel embarrassed or insecure.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

PLEASE CONTINUE ON THE NEXT PAGE

Impact of Cancer – Childhood Survivors Scale (IOC-CS)– Zebrack, 2009

CANCER TREATMENT AND HEALTH CARE

Please mark an ☐ in the one box for each statement that best describes your answer.

	Not at all ▼	A little bit ▼	Some what ▼	Quite a bit ▼	Very much ▼
12. When I have a health problem I know who to see for medical care.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
13. Going to the doctor makes me nervous or anxious.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
14. I am confident that any doctors I see know about the long-term effects of childhood cancer treatment.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
15. It is easy for me to talk to doctors about my cancer history.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
16. I have all the information I need about my cancer, its treatment, and possible long-term effects.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
17. When I need information about cancer I know where to find it.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

PLEASE CONTINUE ON THE NEXT PAGE

Impact of Cancer – Childhood Survivors Scale (IOC-CS)– Zebrack, 2009

HAVING CHILDREN

Please mark an ☒ in the one box for each statement that best describes your answer.

	Not at all ▼	A little bit ▼	Some what ▼	Quite a bit ▼	Very much ▼
20. I am concerned that I may not be able to have children (get pregnant, get someone pregnant).	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
21. I am concerned about my children getting cancer.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
22. I am concerned about whether my children will be healthy.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

WHO ARE YOU?

Please mark an ☒ in the one box for each statement that best describes your answer.

	Not at all ▼	A little bit ▼	Some what ▼	Quite a bit ▼	Very much ▼
23. I have confidence in myself.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
24. I am a cautious or careful person.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
25. Cancer is part of who I am, the person I am today.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
26. I feel I am different than other people my age who have not had cancer.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
27. I feel I am more mature than people my own age.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
28. I am a risk-taker.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
29. I feel in control of my life.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

PLEASE CONTINUE ON THE NEXT PAGE

TALKING AND THINKING ABOUT CANCER

Please mark an ☒ in the one box for each statement that best describes your answer.

	Not at all ▼	A little bit ▼	Some what ▼	Quite a bit ▼	Very much ▼
30. I think about having had cancer.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
31. I would like to forget about having had cancer.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
32. I need to talk about cancer and what I went through.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
33. I feel comfortable talking about cancer.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
34. I wonder why I got cancer.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
35. I wonder why I survived and others do not.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
36. I feel like something I did caused me to get cancer.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
37. I am angry about having had cancer.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
38. People treat me differently after they find out I have had cancer.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
39. I feel like cancer controls my life.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
40. I feel a special bond with people with cancer.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
41. I feel like time in my life is running out.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
42. I am afraid to die.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
43. I worry that I might die at a young age.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

PLEASE CONTINUE ON THE NEXT PAGE

MEANING OF CANCER

Please mark an ☒ in the one box for each statement that best describes your answer.

	Not at all ▼	A little bit ▼	Some what ▼	Quite a bit ▼	Very much ▼
44. Good things have come out of having had cancer.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
45. I learned something about myself because of having had cancer.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
46. Cancer has been the most difficult experience of my life.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
47. Having had cancer makes me think about or question my religious faith, faith in God or a higher power.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

MEMORY AND THINKING

Please mark an ☒ in the one box for each statement that best describes your answer.

	Not at all ▼	A little bit ▼	Somewh at ▼	Quite a bit ▼	Very much ▼
48. It is easy for me to make decisions.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
49. It is easy for me to learn new things.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
50. I have a hard time thinking or concentrating.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
51. I have a hard time remembering things from long ago.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
52. I have trouble remembering things, even for just a few minutes (like directions, phone numbers, etc.)	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

PLEASE CONTINUE ON THE NEXT PAGE

FINANCES AND MONEY

Please mark an ☒ in the one box for each statement that best describes your answer.

Not at all	A little bit	Some what	Quite a bit	Very much	Not applicabl e
▼	▼	▼	▼	▼	▼

55. I have financial problems related to having had cancer.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 8
56. My parents have financial problems related to my cancer and treatment.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 8
57. I have had trouble getting assistance or services that I need, such as insurance, disability or social security benefits, time off from work for doctors' visits, extra time to finish work or exams, specialized medical equipment, etc.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 8

If you would like, please describe your answer to #57 here:

FAMILY

Please mark an ☐ in the one box for each statement that best describes your answer.

	Not at all ▼	A little bit ▼	Some what ▼	Quite a bit ▼	Very much ▼
58. Having cancer brought my family closer together.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
59. I feel guilty for what my family members had to go through when I had cancer.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
60. My mother worries about me.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
61. My father worries about me.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
62. I am comfortable discussing my cancer with my mother.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
63. I am comfortable discussing my cancer with my father.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
64. My mother is comfortable discussing my cancer with me.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
65. My father is comfortable discussing my cancer with me.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

Do you have brothers or sisters?

☐₀ No → please continue on the next page.

☐₁ Yes → please answer the questions below.



	Not at all ▼	A little bit ▼	Some what ▼	Quite a bit ▼	Very much ▼
66. I worry about how my cancer has affected some or all of my brothers and/or sisters.	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
67. I have a brother or sister with problems that might be related to my having had cancer (for example, drug or alcohol problems, learning or school problems, behavior problems, or trouble with the law).	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

Impact of Cancer – Childhood Survivors Scale (IOC-CS)– Zebrack, 2009

Are you currently married, living together as married, or in a significant committed relationship?

☐₁ Yes → skip to QUESTION 72 below

☐₀ No → continue with QUESTION 68 below



Answer if you are NOT married, living together or in a significant relationship.

	Not at all ▼	A little bit ▼	Some- what ▼	Quite a bit ▼	Very much ▼
68. I worry about not having a spouse, partner, boyfriend or girlfriend.	<input type="checkbox"/> ₀	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
69. I worry about telling a potential spouse, partner, boyfriend or girlfriend that I have had cancer.	<input type="checkbox"/> ₀	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
70. I am concerned about how to tell a potential spouse, partner, boyfriend or girlfriend that I may not be able to have children.	<input type="checkbox"/> ₀	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
71. I worry about having sex.	<input type="checkbox"/> ₀	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄

STOP HERE and go to the NEXT PAGE

Please answer the following questions only if you are currently married, living together as married, or in a significant relationship. Otherwise, please stop and go to the next page.

	Not at all ▼	A little bit ▼	Some- what ▼	Quite a bit ▼	Very much ▼
72. If I have a health problem, I feel comfortable talking to my spouse/partner about it.	<input type="checkbox"/> ₀	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
73. I worry about my spouse/partner leaving me if I were to get cancer again.	<input type="checkbox"/> ₀	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
74. I worry about having sex with my spouse/partner.	<input type="checkbox"/> ₀	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄

SOCIALIZING AND BEING WITH FRIENDS

Please mark an ☒ in the one box for each statement that best describes your answer.

	Not at all ▼	A little bit ▼	Some what ▼	Quite a bit ▼	Very much ▼
75. I make friends easily.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
76. I avoid social activities.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
77. I feel left out from my friends' lives or activities.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
78. I feel love and support from my friends.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
79. I feel like I missed out on important life experiences while I had cancer.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

LIFE GOALS

Please mark an ☒ in the one box for each statement that best describes your answer.

	Not at all ▼	A little bit ▼	Some what ▼	Quite a bit ▼	Very much ▼
80. I feel like I have goals in life.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
81. I feel like I know what I have to do to reach my goals.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
82. Having had cancer makes me feel unsure about my future.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
